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TERMINATION OF VENTRICULAR FIBRILLATION IN MAN BY EXTERNALLY APPLIED ELECTRIC COUNTERSHOCK*

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BOSTON

VENTRICULAR fibrillation is usually a rapidly fatal arrhythmia that may occur in cardiac patients, in any patient under anesthesia and in drowning and electrocution. In cardiac patients it is a frequent cause of sudden death in the course of coronary-artery disease, a well recognized mechanism of Stokes–Adams attacks, an uncommon toxic reaction to digitalis, quinidine and procaine amide, an occasional terminating event in ventricular tachycardia and a rare, but dreaded, complication of cardiac catheterization. In the operating room ventricular standstill is the usual initial mechanism of cardiac arrest, but ventricular fibrillation occasionally occurs,[1] particularly during hypothermia or during anesthesia with chloroform or cyclopropane.

Ventricular fibrillation causes an immediate cessation of circulation; it rarely stops spontaneously, and its treatment is unsatisfactory. When it occurs in the operating room, the chest may be opened, and intermittent manual compression of the heart ("cardiac massage") performed to restore circulation. The fibrillation may then terminate spontaneously, after the administration of drugs or after the application of electric current directly to the exposed heart.[2] The defibrillating countershock usually consists of 60-cycle alternating current of 1½ amperes or more (120 to 150 volts) for 0.1 to 0.5 second, applied across large electrodes on the heart.

In the laboratory animal, ventricular fibrillation has also been terminated by the external application of countershock current across the closed chest,[3-8] a procedure with much wider clinical applicability. This paper reports the successful termination of ventricular fibrillation in 4 patients by countershock applied externally across the closed chest and demonstrates that external countershock is an immediately effective, safe and clinically feasible procedure.

APPARATUS AND TECHNIC

The external defibrillator** has a circuit similar to that described for direct defibrillation by MacKay, Mooslin and Leeds.[9] A special 6:1 isolation step-up transformer and a variable autotransformer†† are used to convert the 120-volt line current to a range of 0 to 720 volts. The duration of the current is fixed at 0.15 second by a suitable condenser in a relay circuit. The step-up transformer and the power relay contacts are capable of transferring approximately 12,000 watts (15 amperes at 720 volts) for 0.15 second at 1-second intervals. Copper electrodes, 7.5 cm. in diameter, mounted on heavily insulated handles, were smeared with electrode paste and were held firmly in place against the chest wall at the level of the apex, one to the left of the sternum and the other on the anterior axillary line. In view of the high voltages used, the personnel was instructed not to touch the electrodes or the patient's body, and that one person should not hold both electrodes.

Immediately before application of countershock current, the time constant of the amplifier of the electrocardiograph‡‡ was usually shortened by means of the "Instomatic" switch; as a result the stylus of the instrument was immobilized and protected from the high countershock voltages. This interval, when the action potentials of the heart were not recorded,

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**Manufactured by the Electrodyne Company, Norwood, Massachusetts.

††Variac V20, manufactured by the General Radio Company, Cambridge, Massachusetts.

‡‡A single-channel, direct-wiring instrument, Visocardiette, manufactured by the Sanborn Company, Cambridge, Massachusetts.

is indicated in Figures 1-6 by an interrupted horizontal line. A cardiac pacemaker* was used to stimulate the heart externally when ventricular standstill followed defibrillation.[10-13]

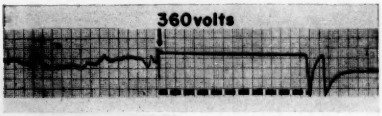

FIGURE 1. *Electrocardiograms (Lead 2) in Case 1. Countershock of 360 volts applied at the arrow, during momentary interruption of the tracing, terminated the fibrillation. When the electric recording was resumed, at the end of the interrupted horizontal line, cardiac arrest was observed.*

CASE REPORTS

Ventricular fibrillation after myocardial infarction, with defibrillation followed by cardiac standstill and death

CASE 1. A 64-year-old woman was hospitalized on August 17, 1955, for a 2d massive myocardial infarction complicated by recurrent pain and increasing congestive heart failure. She suddenly collapsed 5 days later, and an electrocardiograph showed ventricular fibrillation. After 7 minutes of circulatory and respiratory arrest, a single countershock of 360 volts was applied across electrodes on the chest. The ventricular fibrillation was terminated instantaneously, but persistent ventricular standstill followed and heart beats could not be stimulated by the external electric pacemaker (Fig. 1).

Ventricular fibrillation after irregular tachycardia and prolonged circulatory collapse, with 6 defibrillations, each followed by transient ventricular standstill or ventricular beats, and with recurrent fibrillation and death

CASE 2. A 78-year-old man was admitted to the hospital on October 30, 1955, unconscious and in circulatory collapse for about ½ hour. An electrocardiogram on admission showed an irregular tachycardia (Fig. 2*A*). Oxygen, levarterenol (Levophed) and procaine amide (200 mg.) were administered without effect. After 15 minutes a convulsion occurred, and respirations ceased. The electrocardiogram then showed ventricular fibrillation (Fig. 2*B*). After 1 minute of ventricular fibrillation, external electric countershock was applied. Initial shocks of 240 and 360 volts were ineffective (Fig. 2*C*). A 3d shock of 480 volts applied 1½ minutes after the onset of fibrillation was followed by slow ventricular beats (Fig. 2*D*), but fibrillation recurred after 21 seconds. On 5 subsequent occasions over the next 8 minutes, countershocks of 600 and 720 volts (Fig. 2*E, F* and *G*) defibrillated the ventricles. Each time, however, fibrillation recurred within 2 to 30 seconds after periods of cardiac standstill or ventricular beats. Adequate respiratory exchange was not effected; circulatory collapse persisted, and the patient died.

Ventricular tachycardia and fibrillation due to digitoxin, with defibrillation followed by ventricular beats for 5½ minutes and persistent circulatory collapse and death

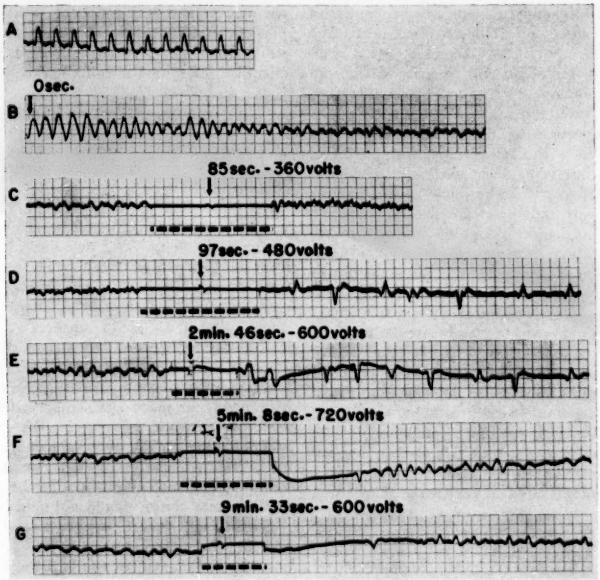

FIGURE 2. *Electrocardiograms (Lead 3) in Case 2, Showing Irregular Tachycardia* (A), *Onset of Ventricular Fibrillation* (B), *Ineffective Countershock* (C) *and Successful Defibrillations Followed by Ventricular Beats* (D *and* E), *Cardiac Standstill and Recurrent Fibrillation* (F *and* G). *The interrupted horizontal lines indicated when the electric activity of the heart was not recorded.*

*Manufactured by the Electrodyne Company, Norwood, Massachusetts.

CASE 3. A 63-year-old man entered the hospital on January 25, 1956, with nausea and vomiting from digitoxin. During the next afternoon pulmonary edema developed, resisting all therapeutic measures. At 7:30 p.m. the blood pressure fell; levarterenol was administered intravenously, but only transient feeble pulses were obtained. An electrocardiogram at 8:00 p.m. showed ventricular tachycardia (Fig. 3*A*). At 8:10 p.m. a convulsive seizure occurred and was followed by apnea, and ventricular fibrillation was observed (Fig. 3*B*). Thirty-three seconds later a countershock of 240 volts was applied across the chest and stopped the fibrillation (Fig. 3*C*). Ventricular beats returned, which were regular and uniform in pattern (Fig. 3*D*). The ventricular rhythm continued for 5½ minutes at 55 to 60 beats per minute, but the patient remained apneic, pulseless and ventricular activity interrupting an idioventricular rhythm of about 30 per minute. He was resuscitated repeatedly from ventricular standstill by brief applications of external stimulation. Continuous electric stimulation for a 14-hour period at rates of more than 40 per minute not only prevented seizures due to ventricular standstill but also suppressed the ectopic activity.

Various drugs were then administered in an attempt to prevent the ectopic ventricular activity by accelerating the idioventricular pacemaker. Epinephrine, isoproterenol and ephedrine accelerated the idioventricular rate, but did not prevent recurrent seizures that were due to short runs of ventricular fibrillation. On 3 occasions major seizures due to prolonged ventricular fibrillation stopped immediately after the application of electric countershock.

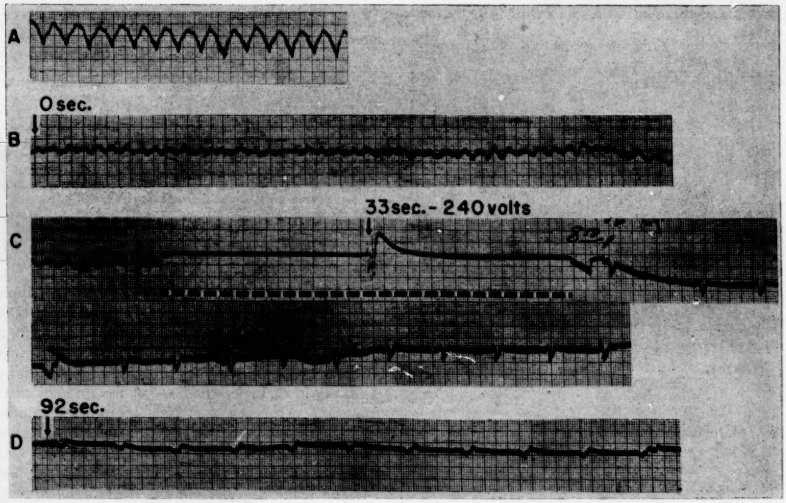

FIGURE 3. *Electrocardiograms (Lead 2) in Case 3, Showing Ventricular Tachycardia* (A), *Ventricular Fibrillation* (B), *and Termination of Fibrillation by Countershock of 240 Volts (at the Arrow), with Resumption of Ventricular Beats* (C) *— the Interrupted Horizontal Line Indicates when the Electric Activity of the Heart Was Not Recorded — and Regular Ventricular Rhythm* (D) *Persisting after Defibrillation for Five and a Half Minutes.*

unresponsive. External electric stimulation evoked electrocardiographic ventricular responses, but no peripheral pulses were felt. Other resuscitative measures of artificial respiration with oxygen and intravenous administration of vasopressor agents were not applied; ventricular fibrillation recurred, and the patient died.

Stokes–Adams attacks due to ventricular standstill and ventricular fibrillation, with successful defibrillation on 3 occasions and termination of ventricular tachycardia on 1, followed by complete recovery

CASE 4. A 67-year-old man entered the hospital on November 17, 1955, because of almost continuous Stokes–Adams attacks. He had been well until 2 months previously, when seizures began at about weekly intervals and a slow pulse was noted. Two days before admission the seizures increased in frequency.

On admission he was having a seizure and was pulseless. While the electric pacemaker was being obtained, resuscitation was unsuccessfully attempted by striking the chest and by cardiac puncture. Then external electric stimulation[10-13] immediately revived the patient, and spontaneous beats returned. Electrocardiograms showed recurrent episodes of ventricular standstill, as well as frequent multifocal ectopic

First defibrillation. On December 4 the basic idioventricular rate ranged from 43 to 50 per minute (Fig. 4*A*), with multifocal ventricular activity and brief runs of ventricular tachycardia at 100 per minute. At 9:00 p.m. (1 hour after 25 mg. of ephedrine orally and 4 hours after 10 mg. of isoproterenol sublingually) the patient suddenly had a major convulsive seizure; respirations and heart beat ceased, and he appeared dead. Two minutes after the onset of the seizure a continuous electrocardiogram was started and showed ventricular fibrillation (Fig. 4*B*). The electrodes of the external defibrillator were applied to the chest wall. Electric countershocks of 180, 240, and 270 volts were applied 47 (Fig. 4*C*), 92 and 112 seconds, respectively, after the beginning of the recorded fibrillation, without effect. At 135 seconds (Fig. 4*D*) another shock of 270 volts was applied; when cardiac activity was recorded again 3 seconds later, ventricular tachycardia was present and persisted until 150 seconds, when a shock of 300 volts was applied. For the next 17 seconds electric activity of the heart was not recorded and is therefore not illustrated. During this time the patient remained syncopal and pulseless. External electric stimulation with a cardiac pacemaker was started, since the ventricles was assumed to be in standstill; ventricular responses (V) were then observed (Fig. 4*E*) to every other

stimulus (E). After 13 seconds rapid spontaneous ventricular beats reappeared; this ventricular tachycardia persisted for 90 seconds (Fig. 4*F*), and then stopped spontaneously, and was followed by the usual slow idioventricular rhythm (Fig. 4*G*). The total elapsed time from the onset of the seizure to the return of idioventricular rhythm was about 7 minutes. Shortly thereafter the blood pressure was 206/74, and the patient was alert and responsive.

Second defibrillation. Because of persistent multifocal ventricular activity, the isoproterenol and ephedrine were stopped. Nevertheless, the ectopic activity was still present

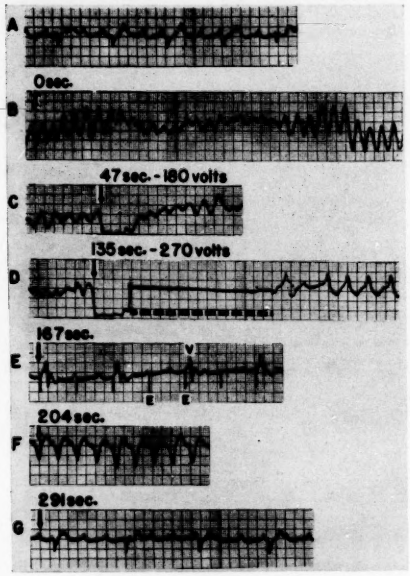

FIGURE 4. *Electrocardiograms (Lead 2) on December 4 in Case 4.*

The indicated times are from beginning of the continuous electrocardiogram, two minutes after the onset of the episode. The interrupted horizontal line indicates when the electric activity of the heart was not recorded.

on December 6 (Fig. 5*A*). At 9:20 a.m., a major seizure occurred, and a continuous electrocardiogram started 1½ minutes later showed ventricular fibrillation. Countershocks of 300 and 312 volts were applied 37 (Fig. 5*B*) and 45 seconds, respectively, after the beginning of the recorded fibrillation but were ineffective. At 70 seconds (Fig. 5*C*) a shock of 324 volts was applied. In 1 second, when the cardiac activity was recorded again, the rhythm had changed to ventricular tachycardia (Fig. 5*C*, end). The tachycardia lasted for 23 seconds, and then stopped spontaneously, and was followed by ventricular standstill (Fig. 5*D*). Electric stimuli (E) of 50 volts, begun near the end of the tachycardia, were ineffective. When ventricular standstill persisted, the stimuli (E) were increased to 75 volts at 106 seconds and immediately produced (Fig. 5*E*) ventricular responses (V). Fifteen seconds later spontaneous idioventricular rhythm returned (Fig. 5*F*). Shortly thereafter the patient had completely recovered, and the blood pressure was 240/98.

During the next 5 days, 9 seizures occurred. Several stopped promptly after electric stimulation, but others did not respond. Electrocardiograms taken in 2 of these episodes showed ventricular fibrillation that terminated spontaneously. During this period the ventricular rate ranged from 28 to 80 (Fig. 6*A*), and the rhythm was interrupted by frequent multifocal, ectopic ventricular activity. Atropine, 0.6 mg. at 4-hour intervals, was followed by excessive ventricular acceleration and ectopic ventricular activity, so that the drug was stopped.

Third defibrillation. At 10:40 a.m. on December 11, 3 hours after the administration of 0.6 mg. of atropine, another major seizure occurred. Within 1 minute of its onset a continuous electrocardiogram was started and showed ventricular fibrillation. An external countershock of 300 volts applied 71 seconds later was ineffective (Fig. 6*B*). A 2d shock of 360 volts was applied at 87 seconds (Fig. 6*C*). Within 1 second, when electric activity was recorded again, cardiac standstill was seen. This persisted for 12 seconds, whereupon external stimulation at 60 volts was started and produced effective ventricular beats (Fig. 6*C*). After 15 seconds, spontaneous ventricular beats reappeared, and the regular idioventricular rhythm resumed within a few seconds (Fig. 6*D*). The patient regained consciousness promptly, and the blood pressure returned to its previous level.

Ephedrine sulfate (25 mg. every 4 hours) and atropine sulfate (0.6 mg. 4 times a day) were administered orally, and the multifocal ventricular activity lessened. With larger doses of ephedrine the ectopic activity increased. After having been free of seizures for 9 days, the patient was discharged on December 20, when he was up and about, felt well and insisted on going home before Christmas. He had remained well for 3 months when last seen.

DISCUSSION

These 4 cases demonstrate that externally applied electric countershock is an immediately effective, safe and clinically feasible procedure. The efficacy of this technic in defibrillating the ventricles was clearly established by the repeated observations—11 times in these 4 patients—of the immediate termination of ventricular fibrillation after countershock. On one occasion (Case 4, December 4) ventricular tachycardia also ceased after external countershock, suggesting that this procedure may prove valuable clinically in stopping other arrhythmias as well as ventricular fibrillation. We have been able to stop atrial fibrillation, atrioventricular nodal tachycardia and ventricular tachycardia in the laboratory animal with this technic.[8]

The amounts of externally applied current necessary to stop ventricular fibrillation in these patients ranged from 240 to 720 volts. The complete recovery in Case 4 after repeated countershock indicates that external defibrillation can be accomplished without ill effect to the patient. Several physicians were involved in applying these potentially dangerous currents to the patients; with prior instruction and a well devised instrument, the procedure appeared safe for all concerned.

As with external resuscitation from ventricular standstill with the cardiac pacemaker, successful defibrillation depends on immediate recognition of the emergency and prompt application of the external defibrillator. Although external countershock can be applied easily and quickly, delays in its application constitute the major limitation of successful resuscitation. In Case 4, the resuscitations were accom-

plished within two to four minutes of fibrillation, since its probability had been recognized and the defibrillator was at hand. In the 3 patients who died, circulation had been ineffective for seven minutes or more before defibrillation.

Defibrillation may be followed by ventricular standstill or recurrent fibrillation, especially when associated with anoxia from prolonged circulatory arrest. It may then be necessary to apply an external cardiac pacemaker, to use the defibrillator repeatedly and to employ other resuscitative measures such as vasopressor agents and artificial respiration with oxygen.

the active phase of Stokes–Adams disease. Under these circumstances, especially when fibrillation is apt to recur, external countershock may offer the only effective therapy. Thoracotomy with cardiac massage was not considered in these elderly patients with severe cardiac disease; even in better-risk patients, this procedure is thought inadvisable except in the operating room or similar favorable situations.[15] When unexpected cardiac arrest occurs in the operating room, external electric stimulation[16] and external electric defibrillation comprise a combined technic for cardiac resuscitation before recourse to the more formidable and traumatic proce-

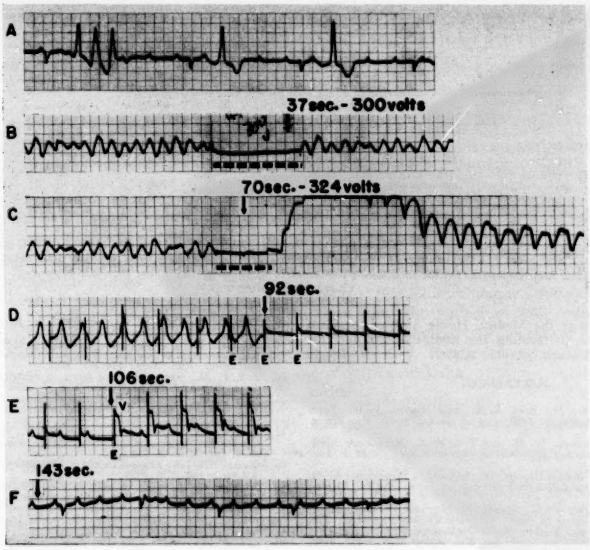

FIGURE 5. *Electrocardiograms (Lead 2) on December 6 in Case 4.*
The indicated times are from the beginning of the continuous electrocardiogram, one and a half minutes after the onset of the episode. The interrupted horizontal lines indicated when the electric activity of the heart was not recorded.

The experience in Case 4 is pertinent to the question of the safety of external electric stimulation. An electric stimulus applied directly to the heart in animals may produce multiple ventricular beats and ventricular fibrillation.[14] In this patient electric stimulation was never observed to produce ventricular fibrillation, even though it was applied for ventricular standstill on numerous occasions during periods when multifocal activity and fibrillation were frequent.

In these 4 patients, ventricular fibrillation occurred in the course of an acute myocardial infarction, after the intravenous administration of procaine amide for a rapid arrhythmia, from digitoxin toxicity and in

dure of cardiac massage. Continuous cardiac monitoring in the operating room would enhance the likelihood of successful external resuscitation by providing immediate recognition of the onset and mechanism of the arrest.

SUMMARY

Ventricular fibrillation was terminated 11 times in 4 patients by externally applied electric countershock. These episodes occurred in the course of an acute myocardial infarction, after the intravenous administration of procaine amide for a rapid arrhythmia, in digitoxin intoxication and in Stokes–Adams disease. The patient with Stokes–Adams dis-

ease, who was defibrillated promptly on 3 separate occasions, recovered completely.

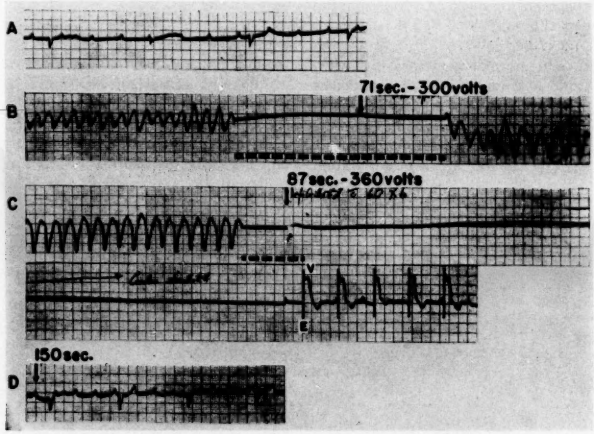

FIGURE 6. *Electrocardiograms (Lead 2) on December 11 in Case 4.*

The indicated times are from the beginning of the continuous electrocardiogram, one minute after the onset of the episode. The interrupted horizontal lines indicated when the electric activity of the heart was not recorded. The two strips of C *are continuous.*

We are indebted to the Medical House Staff of the Beth Israel Hospital for performing the defibrillations and for obtaining the electrocardiographic records.

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THE RESPONSE TO ACETYLSTROPHANTHIDIN*

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PHILADELPHIA

CARDIAC failure is frequently precipitated by a noncardiac illness. Although digitalis is used to restore and maintain compensation, the self-limiting nature of the precipitating event or its response to specific therapy may make it difficult or impossible to determine the effects of digitalis. To give a so-called digitalizing dose at one time does not answer this problem because almost always no immediate effects are seen.[1,2] Dissipation of symptoms and signs of cardiac failure requires a variable time, measurable in days, weeks or even months. One rightly hesitates to increase the so-called digitalizing dose for fear of producing prolonged toxicity or death.

To determine the specific effects of digitalis in various clinical illnesses that are transient, it is necessary to use a preparation whose effect is rapid and lasts for a very short time. Such a preparation is acetylstrophanthidin, a synthetic ester of the cardiac aglycone strophanthidin.[3]

The purpose of this study is to determine the response of the normal and of the abnormal heart to acetylstrophanthidin and the modifications of these responses by noncardiac illness and by previous digitalis medication.

MATERIAL AND METHODS

Thirty patients were studied, 9 males from forty-five to seventy-six and 21 females from thirty-nine to eighty-three years of age. One was studied on 3 different occasions, and another on 2.

Two had no heart disease, 22 arteriosclerotic heart disease, 1 malignant hypertension, 4 rheumatic heart disease, and 1 heart disease of unknown cause.

After a 12-lead electrocardiogram and after a long tracing of the lead that showed best either the P wave or the arrhythmia, acetylstrophanthidin was given intravenously. Subsequent tracings were obtained frequently, usually at one-minute intervals, and always before each succeeding dose of the drug. The final electrocardiogram was taken at least fifteen minutes and frequently two hours after the last dose of acetylstrophanthidin. In many cases electrocardiograms were taken the next day.

Ampoules containing 1 ml. of a 29 per cent alcoholic solution of 0.6 mg. (3 cat units) of acetylstrophanthidin¶ were used. The drug was given either undiluted or diluted with 5 per cent glucose in water or with 0.9 per cent saline solution. The initial dose varied from 0.15 to 0.6 mg. Subsequent doses, if given, varied from 0.1 to 0.6 mg. at intervals of one to fifteen minutes. Selections of dose and of interval between doses were mainly arbitrary but influenced by knowledge of the clinical state, of previous digitalis medication, of electrocardiographic findings and of onset and duration of the effects of acetylstrophanthidin.

The cases were classified according to the presence or absence of heart disease and previous digitalis medication.

RESULTS

Group 1 (No Heart Disease and No Previous Digitalis)

Of the 2 patients in this group, 1 had no organic disease, and the other received acetylstrophanthidin during a bout of renal failure that occurred after a prostatectomy; this patient had a blood urea nitrogen of 74 mg. per 100 ml., and a carbon dioxide combining power of 33.5 vol. per 100 ml. The serum chloride was 82.8 milliequiv., the sodium 123.6 milliequiv., and the potassium 5.48 milliequiv. per liter.

The control electrocardiogram in each subject was normal. Each received a total dose of 2.4 mg. of acetylstrophanthidin, with no significant change in either.

Group 2 (Heart Disease, with No Previous Digitalis)

Of the 9 patients in this group (Table 1) 2 had heart failure. One (D.M.) with atrial fibrillation, whose failure was precipitated by pulmonary infarction, was given a total dose of 2.4 mg. No significant change occurred. Another (M.D.), who had acute pulmonary edema of unknown cause, was given a total dose of 1.4 mg. In two hours, slowing of the sinus mechanism from 100 to 70 per minute resulted.

The other 7 were compensated. Two had atrial fibrillation. One (J.L.) with right-bundle-branch block, had a regular ventricular rate of 140 per minute that, after 0.6 mg., slowed to an irregular ventricular rate of 100 per minute and, after 1.8 mg., to 80 per minute. A ventricular premature beat appeared twenty-five minutes after the final dose of acetylstrophanthidin. The other (C.B.) had an irregular ventricular rate of 75 per minute, and after 1.2 mg. had been given, dizziness, fainting, nausea and vomiting developed. The electrocardiogram showed a slightly prolonged pause followed by a QRS complex different in configuration from the usual complexes, and shorter in duration. The ventricular rate slowed to 65 per minute. Nausea and

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¶Kindly supplied by Dr. B. L. Martz, of the Lilly Research Laboratories, Indianapolis, Indiana.

vomiting, perhaps related to underlying renal disease, lasted for five days.

Three had sinus rhythm. As much as 2.7 mg. was given, with no effect but a 10 per cent decrease in rate. One (A.H.) of the 3 had had ventricular bigeminy in the past, and after 0.3 mg. had been given, this arrhythmia again developed, but succeeding doses to a total of 2.7 mg. had no other significant effect.

The eighth (A.K.) had atrioventricular rhythm. A ventricular premature beat occurred after 1.2 mg. but did not recur after additional acetylstrophanthidin. A notch did appear at J, suggesting the possibility of a lower pacemaker.

The last patient (E.W.), who had paroxysmal atrial tachycardia, was converted to normal sinus rhythm twenty-five minutes after a total dose of 0.6 mg.

TABLE 1. *Effect of Acetylstrophanthidin on Patients in Group 2.*

SUBJECT	AGE	SEX	DIAGNOSIS	RHYTHM & RATE	
				CONTROL	FINAL
	yr.				
D.M.	64	F	None made (patient had enlarged heart, with heart failure from pulmonary infarction)	Atrial fibrillation; irregular ventricular rate of 130/min.	Atrial fibrillation; irregular ventricular rate of 130/min.
M.D.	55	M	Aortic stenosis; enlarged heart; pulmonary edema.	Sinus rhythm; rate of 100/min.	Sinus rhythm; rate of 70/min.
J.L.	65	M	Aortic stenosis; enlarged heart.	Atrial fibrillation; regular ventricular rate of 140/min.; right-bundle-branch block.	Atrial fibrillation; irregular ventricular rate of 80/min.; right-bundle-branch block.
C.B.	71	F	Aortic stenosis; enlarged heart.	Atrial fibrillation; irregular ventricular rate of 75/min.	Atrial fibrillation; irregular ventricular rate of 65/min.
J.K.	64	M	Aortic stenosis; enlarged heart.	Sinus rhythm; rate of 107/min.	Normal sinus rhythm; rate of 94/min.
M.L.	54	F	Myocardial infarction; enlarged heart.	Normal sinus rhythm; rate of 90/min.	Normal sinus rhythm; rate of 80/min.
A.H.	48	M	Aortic stenosis; enlarged heart.	Normal sinus rhythm; rate of 75/min.	Normal sinus rhythm; ventricular bigeminy; rate of 70/min.
A.K.	45	M	Malignant hypertension; enlarged heart.	Atrioventricular rhythm; rate of 70/min.	Atrioventricular rhythm; rate of 70/min.
E.W.	83	F	Aortic stenosis; paroxysmal atrial tachycardia.	Paroxysmal atrial tachycardia; rate of 200/min.	Normal sinus rhythm; rate of 80/min.

Group 3 (Heart Disease, with Previous Digitalis)

There were 15 patients in this group (Table 2).

Six had an obvious factor precipitating failure. Acetylstrophanthidin produced heart block in 1 with sinus rhythm and a 20 per cent slowing of the ventricular rate in 2 with atrial fibrillation. The others showed either no change or an increase in ventricular rate.

One (E.I.) of the 6 was given acetylstrophanthidin on three separate occasions. He was receiving 0.1 gm. of digitalis daily and entered the hospital because of heart failure precipitated by pulmonary infarction. He was given 3.5 mg. of Digoxin over a period of two days. Immediately before the administration of acetylstrophanthidin, an electrocardiogram (Fig. 1) showed atrial fibrillation, with an irregular ventricular rate of 100 per minute and frequent bidirectional ventricular extrasystoles. Five minutes after 0.6 mg. of acetylstrophanthidin, ventricular bigeminy occurred, with unidirectional ventricular premature beats and constant coupling. Ventricular premature beats then disappeared. At thirty minutes, ventricular tachycardia occurred transiently; at thirty-eight minutes, it was constant. Procaine amide abolished the ventricular tachycardia. Digitalis preparations were then discontinued. Five days later, the patient had another bout of heart failure. The control tracing showed atrial fibrillation and an irregular ventricular rate of 150 per minute. A total dose of 1.8 mg. of acetylstrophanthidin was given, without evidence of toxicity except for one ventricular premature beat twelve minutes after cessation of the drug. The final rate was 74 per minute. He was then digitalized with digitoxin. Ten days later, when asymptomatic, he was again given acetylstrophanthidin. The control tracing showed atrial fibrillation with an irregular ventricular rate of 72 per minute. After 1.5 mg., a ventricular premature beat occurred. An additional 0.15 mg. produced more ventricular extrasystoles. The final rate was 100 per minute.

Four patients had no obvious factor precipitating failure. Acetylstrophanthidin produced slowing of

the rate in 1 with atrial fibrillation (H.F.). In another (L.R.), with sinus rhythm and left-bundle-branch block, first-degree block developed after 0.6 mg. (Fig. 2). After an additional 0.15 mg., the PR interval lengthened, and alternate atrial beats were blocked. These changes were followed by a return to normal of the QRS complexes and the occurrence of complete heart block. Within minutes, sinus rhythm reappeared. On the following day, the PR interval was still prolonged, but left-bundle-branch block had reappeared. In the remaining 2 patients, administration of acetylstrophanthidin was followed by an increase in ventricular rate, owing in 1 with atrial fibrillation (I.T.) to ventricular tachycardia and in 1 with sinus rhythm (F.L.) to ventricular bigeminy and sinus tachycardia.

Table 1 *(Concluded).*

Subject	Method of Administration	Total Dose	Initial Toxicity		Effect of Additional Acetylstrophanthidin (If Given)	Duration of Effect
			dose	manifestation		
		mg.	*mg.*			
D.M.	0.5 mg. in 5% glucose in water every 15 min.	2.4	—	—	—	—
M.D.	0.1 mg. in physiologic saline solution every 1-5 min.	1.4	—	—	—	—
J.L.	0.6 mg. initially, followed by 0.3 mg. every 15 min.	1.8	1.8	Ventricular premature beat	—	Transient
C.B.	0.6 mg. every 5 min.	1.2	1.2	Dizziness; nausea & vomiting; nodal beat.	—	5 days (nausea & vomiting); transient (nodal beat).
J.K.	0.3 mg. in physiologic saline solution every 15 min.	1.8	—	—	—	—
M.L.	0.15 mg. every 5 min.	2.25	—	—	—	—
A.H.	0.3 mg. every 15 min.	2.7	0.3	Ventricular bigeminy, unidirectional, with constant coupling	Unchanged except for slowing of rate & increase in coupling	<24 hr.
A.K.	0.3 mg. every 10-25 min.	1.5	1.2	Ventricular premature beat	Disappearance of ventricular premature beat; possible shift to lower pacemaker.	—
E.W.	0.15 mg. every 5 min.	0.6	—	—	—	—

Five others, 4 with atrial fibrillation and 1 with sinus rhythm, showed no significant change in rate.

In contrast to the rarity of any therapeutic effect, toxicity almost always occurred.

Nausea developed in 3 patients. Two of these 3 showed cardiac toxicity simultaneously.

Two had first-degree block as the first sign of toxicity. In 1 (M.T.), although additional drug was not given, increased heart block and ventricular bigeminy occurred for a period of thirty minutes. In the other (L.R.) complete heart block appeared after an additional 0.15 mg.

In 2 cases undirectional ventricular tachycardia developed. One (E.I.) was discussed above. In the other (H.F.) the control tracing showed atrial fibrillation with left-bundle-branch block and an irregular ventricular rate of 100 per minute. After 0.6 mg., a few ectopic beats of a right-bundle-branch-block pattern appeared. Additional drug resulted in the regular and successive occurrence of these beats that disappeared spontaneously in five minutes.

Two patients had bidirectional ventricular tachycardia. One (I.T.) showed in the control tracing atrial fibrillation with at first a regular and then an irregular ventricular rate of 60 per minute and with frequent, multiform ventricular extrasystoles. Five minutes after the administration of 0.15 mg., ventricular tachycardia with inverted QRS complexes occurred. This was shortly followed by transient ventricular bigeminy that was unidirectional, with constant coupling, and then by the reappearance of ventricular tachycardia, with upright QRS complexes. An additional 0.15 mg. resulted in bidirectional ventricular tachycardia that persisted for approximately sixteen minutes. The other patient, with bidirectional ventricular tachycardia (E.K.), was admitted to the hospital because of persistent chest pain, dyspnea and disorientation of five days' duration. She had an acute myocardial infarction and an enlarged heart. Her physician gave her 1.6 gm. of digitalis over a period of five days. A control tracing (Fig. 3) showed indefinite P waves and a regular ventricular rate of 170 per minute. Ten minutes after the administration of 0.15 mg., bidirectional ventricular tachycardia appeared; 50 mg. of procaine amide was given, without effect. One min-

ute later, an additional 50 mg. was given. This was immediately followed by ventricular fibrillation and death.

so in the other. Occasionally, ventricular extrasystoles occurred in succession. Additional acetylstrophanthidin, if given, resulted in increased extrasys-

TABLE 2. *Effect of Acetylstrophanthidin on Patients in Group 3.*

SUBJECT	AGE	SEX	DIAGNOSIS	PREVIOUS DIGITALIS	RHYTHM & RATE	
					CONTROL	FINAL
	yr.					
E.I.	54	M	Coronary-artery disease; pulmonary infarction; enlarged heart, with failure.	0.1 gm. daily for years; 3.5 mg. of Digoxin in 2 days.	Atrial fibrillation; irregular ventricular rate of 100/min., with frequent bidirectional ectopic ventricular beats.	Atrial fibrillation; irregular ventricular rate of 85/min.
				None for 5 days*	Atrial fibrillation; irregular ventricular rate of 150/min.	Irregular ventricular rate of 74/min.
				1.9 mg. (digitoxin) in 10 days†	Atrial fibrillation; irregular ventricular rate of 72/min.	Irregular ventricular rate of 100/min.
E.M.	73	F	Coronary-artery disease; enlarged heart, with failure; cerebrovascular accident (coma).	0.1 gm. daily for 6 wk.	Atrial fibrillation; irregular ventricular rate of 90/min.; 3 ventricular premature beats.	Atrial fibrillation; irregular ventricular rate of 70/min.; 4 ventricular premature beats.
M.W.	45	F	Rheumatic heart disease; enlarged heart, with failure; pulmonary infarction.	0.1 gm. daily for months	Atrial fibrillation; irregular ventricular rate of 60/min.	Atrial fibrillation; irregular ventricular rate of 60/min.
E.K.	72	F	Acute myocardial infarction; enlarged heart, with heart failure.	1.6 gm. in 5 days	Atrioventricular dissociation; regular rate of 170/min.	Bidirectional ventricular tachycardia; rate of 210/min.
M.P.	70	F	Coronary-artery disease; enlarged heart, with failure; diabetes.	0.1 gm. daily for years	Normal sinus rhythm; rate of 75/min.; 1 ventricular premature beat.	Normal sinus rhythm; rate of 75/min.
M.T.	39	F	Rheumatic heart disease; mitral stenosis; enlarged heart, with failure.	0.1 gm. daily for 1 wk.	Normal sinus rhythm; rate of 80/min.	Sinus rhythm; 1st-degree & 2d-degree block (Wenckebach); rate of 40/min.
H.F.	71	F	Coronary-artery disease; aortic stenosis; enlarged heart; residua of cardiovascular accident.	0.1 gm. daily for years	Atrial fibrillation; irregular ventricular rate of 100/min.; left-bundle-branch block.	Atrial fibrillation; irregular ventricular rate of 70/min.; left-bundle-branch block.
I.T.	82	F	Aortic stenosis; enlarged heart.	0.1 gm. daily for months	Atrial fibrillation; regular & then irregular rate of 60/min., with multiform ectopic beats.	Bidirectional ventricular tachycardia; rate of 100/min.
F.L.	48	F	Coronary-artery disease; enlarged heart.	0.1 gm. daily for months	Sinus rhythm; rate of 110/min.	Sinus rhythm; rate of 120/min.
L.R.	69	F	Aortic stenosis	6 mg. of Gitalin in 3 days	Normal sinus rhythm; rate of 80/min.; left-bundle-branch block.	Sinus rhythm; rate of 60/min.; 1st-degree block; normal QRS complex.
M.E.	44	F	Rheumatic heart disease; mitral stenosis; myocardial infarction; enlarged heart.	0.1 gm. daily for years	Atrial fibrillation; irregular ventricular rate of 60/min.	Atrial fibrillation; irregular ventricular rate of 60/min.
E.N.	60	F	Aortic stenosis; enlarged heart.	0.8 mg. of digitoxin intramuscularly 8 hr. earlier	Atrial fibrillation; irregular ventricular rate of 150/min.; 1 ventricular premature beat.	Atrial fibrillation; irregular ventricular rate of 150/min.; ectopic beats.
F.D.	47	F	Rheumatic heart disease; mitral stenosis; myocardial infarction; enlarged heart.	0.1 gm. daily for years	Atrial fibrillation; irregular ventricular rate of 60/min.	Atrial fibrillation; irregular ventricular rate of 70/min.
F.C.	63	F	Aortic stenosis; enlarged heart; diabetes.	0.1 gm. daily for years	Atrial fibrillation; irregular ventricular rate of 65/min.	Atrial fibrillation; irregular ventricular rate of 65/min.; ectopic beats.
V.R.	45	M	Aortic stenosis; enlarged heart.	0.1 gm. daily for months	Sinus rhythm; rate of 88/min.; 1st-degree block.	Sinus rhythm; rate of 80/min.; 1st-degree block.

* 5 days later — patient in heart failure.
†15 days later — patient asymptomatic.

Ventricular bigeminy developed in 6 cases. Of these 6, the ventricular extrasystoles were unidirectional with constant coupling in 5 and predominantly

toles in all except 1 patient (V.R.), who had a single ventricular premature beat and pre-existing first degree heart block. Additional drug did not pro-

duce any ventricular extrasystole. In the others, ventricular extrasystoles increased in number and were often consecutive. Frequently, the ventricular extrasystoles were polymorphous.

Digoxin until nausea was produced. No cardiac toxicity was present.

In all, toxicity followed the administration of 0.15 to 0.6 mg. of acetylstrophanthidin.

TABLE 2 *(Concluded).*

SUBJECT	METHOD OF ADMINISTRATION	TOTAL DOSE	INITIAL TOXICITY		EFFECT OF ADDITIONAL ACETYLSTROPHANTHIDIN (IF GIVEN)	DURATION OF EFFECT
			DOSE	MANIFESTATION		
		mg.	*mg.*			
E.I.	0.6 mg. in 5% glucose in water	0.6	0.6	Ventricular premature beats in bigeminy (unidirectional, constant coupling); frequent ectopic beats; ventricular tachycardia for 2 min. after 38 min.; nausea.	—	40 min. (cardiac irregularities); <24 hr. (nausea).
	0.3 mg. every 12 min.	1.8	1.8	Ventricular premature beat	—	Transient
	0.3 mg. every 15 min.	1.8	1.5	Ventricular premature beat	Increased ventricular premature beats, occasionally bidirectional & rarely in succession	25 min.
E.M.	0.3 mg. every 15 min.	1.8	0.3	Ventricular premature beats, different in direction from control	Increased ventricular premature beats — rarely bidirectional	>15 min.
M.W.	0.3 mg. every 15 min.	0.6	0.6	Ventricular premature beats (bigeminal); occasional premature beats in succession; majority unidirectional, with constant coupling.	—	2 min.
					—	13 min.
E.K.	0.15 mg.	0.15	0.15			
M.P.	0.15 mg. every 5 min.	1.65	1.65	Nausea		24 hr.
M.T.	0.1 mg. every 5 min.	1.05	1.05	1st-degree & 2d-degree block (Wenckebach); nausea.	Additional ventricular bigeminy, unidirectional, with constant coupling; complete heart block; nausea.	>30 min. (cardiac irregularity); 24 hr. (nausea).
H.F.	0.3 mg. every 15 min.	1.5	0.6	Ventricular premature beats (right-bundle-branch block)	Increased number of ventricular complexes of right-bundle-branch-block type, successive & regular	5 min.
I.T.	0.15 mg. every 15 min.	0.3	0.15	Ventricular tachycardia; ventricular bigeminy (unidirectional, with constant coupling).	Ventricular tachycardia (bidirectional)	>16 min.
F.L.	0.15 mg. every 5 min.	0.3	0.3	Ventricular premature beats; bigeminy (unidirectional, with constant coupling).	—	2 min.
L.R.	0.15 mg. every 5 min.	0.75	0.75	1st-degree block	2:1 block; complete heart block; return to normal of ventricular complex.	15 min. (complete heart block)
M.E.	0.1 mg. followed by 0.2 mg. every 5-10 min.	0.9	—	—	—	—
E.N.	0.3 mg.	0.3	0.3	Ventricular premature beats (unidirectional, with inconstant coupling); 2 ectopic beats in succession.	—	10 min.
F.D.	0.6 mg. followed by 0.3 mg. every 15 min.	1.2	0.6	Ventricular premature beats; bigeminy (unidirectional, with constant coupling).	Bigeminy (bidirectional)	2 min.
F.C.	0.15 mg. every 5 min.	2.1	0.15	Ventricular premature beat	Increased ventricular premature beats; ectopic beats.	<24 hr.
V.R.	0.1 mg. in physiologic saline solution every 5 min.	0.8	0.6	Ventricular premature beat	Disappearance of ventricular premature beat	

* 5 days later — patient in heart failure.
†15 days later — patient asymptomatic.

Group 4 (Heart Disease, with Previous Digoxin)

The 5 patients in this group (Table 3) were given

In 1 with atrial fibrillation (H.F.) 2 consecutive ectopic beats of a right-bundle-branch-block pattern

developed five minutes after 0.15 mg. An additional 0.15 mg. produced a regular series of these ectopic beats that disappeared spontaneously. On a previous occasion, on a dose of 0.1 gm. of digitalis daily, similar ectopic beats were produced by 0.6 mg. of acetylstrophanthidin, becoming consecutive and regular after 1.5 mg.

One patient with accelerated atrioventricular conduction and normal QRS complex (J.E.) had ventricular extrasystoles after 0.6 mg. Additional drug resulted in many multiform ventricular extrasystoles. The ventricular extrasystoles then quickly occurred in bigeminy and were predominantly unidirectional, with constant coupling. Toxicity disappeared in fifteen minutes.

Of the remaining 3 patients, 1 (L.N.) manifested complete heart block with increased nausea after 0.45 mg. There was no preceding cardiac toxicity. Complete heart block disappeared spontaneously in three minutes. In another (D.H.), after 0.45 mg., ventricular extrasystoles developed and soon occurred in bigeminy. Ventricular bigeminy was multiform, with inconstant coupling. Additional drug caused nausea and vomiting, first-degree heart block and more ventricular extrasystoles. The ventricular extrasystoles disappeared spontaneously in ten minutes, but the first-degree heart block persisted for twenty-four hours.

In the last patient (H.R.) increased nausea and vomiting followed 0.45 mg. and became intolerable after an additional 0.15 mg. No sign of cardiac toxicity appeared.

Discussion

These studies indicate that acetylstrophanthidin has no recognizable electrocardiographic effect on the normal heart even after 2.4 mg. — an amount that is double the digitalizing dose recommended by Enselberg, Altchek and Hellman.[4] Nevertheless, a functional arrhythmia, such as paroxysmal atrial tachycardia, may be converted to normal sinus rhythm within twenty-five minutes with as little as 0.6 mg.

The effect of acetylstrophanthidin, if any, is first seen within half a minute to five minutes and becomes maximal in about ten minutes.[5] This rapid action obviates the effect of time, which is so important for subsidence of precipitating causes of cardiac failure.

The manifestations of cardiac failure cannot, of course, disappear in so short a time. A dose of acetylstrophanthidin is therefore regarded as sufficient if adequate slowing of the ventricular rate occurs or if signs interpreted as toxic appear.

In the absence of cardiac failure, patients with heart disease and sinus rhythm can tolerate a total dose of acetylstrophanthidin as large as that tolerated by those without heart disease. Even those with

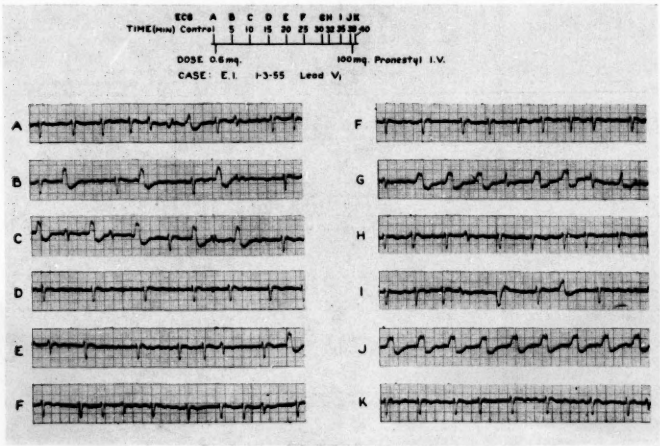

Figure 1. *Lead V_1 in a Fifty-four-Year-Old Man with Coronary-Artery Disease, Pulmonary Infarction and Heart Failure Previously Digitalized with Digoxin.*

The control tracing shows atrial fibrillation, with an irregular rate of 100 per minute and frequent ventricular extrasystoles. Five minutes after 0.6 mg., ventricular bigeminy occurred, with unidirectional ventricular premature beats and constant coupling (B). *Ventricular extrasystoles disappeared* (F). *At thirty minutes, ventricular tachycardia occurred transiently* (G). *At thirty-eight minutes, it was permanent* (J). *Procaine amide abolished the tachycardia* (K).

atrial fibrillation may show no significant effect. Apparently, adequate atrioventricular block is not significantly influenced by large doses of acetylstrophanthidin. Perhaps, for this reason, patients of this sort exhibit no untoward effect when a so-called maintenance dose of digitalis is discontinued.

On the other hand, in the presence of cardiac failure, acetylstrophanthidin may rapidly produce significant electrocardiographic changes. The amount of the drug necessary to produce these changes depends also on the clinical cause of failure. When failure is precipitated by a noncardiac illness, the dose necessary for significant electrocardiographic effects may be greatly increased. Indeed, at times, no effect may be recognizable even after a very large total dose. Thus, 1 patient whose failure was precipitated by pulmonary infarction had no significant electrocardiographic response after the administration of 2.4 mg. On the other hand, the dose needed to produce an adequate response in those in failure for which no recognizable precipitating cause was found was much less. Similar observations were made long ago by Wyckoff and Goldring,[6] who reported that patients with atrial fibrillation and fever required a greater amount of ouabain to reduce the ventricular rate than those without fever. In persons with static disability, the digitalizing dose of acetylstrophanthidin is 1.2 mg. If failure is rapid in development, the effective dose is larger. In such circumstances, it is possible that a precipitating cause of failure has been overlooked.

Usually, much smaller doses of acetylstrophanthidin are needed for significant electrocardiographic effects in patients who have already had digitalis. This difference in dose forms the basis of the acetylstrophanthidin tolerance test introduced by Lown and Levine.[1] This test is similar in principle to the Hatcher and Brody cat method for the assay of digitalis.[7] Lown and Levine recognize the potential dangers of their test and stress the need for constant electrocardiographic surveillance.

The difference in electrocardiographic response to acetylstrophanthidin of patients with and those without any evident cause of the heart failure is as true for those receiving digitalis as for those who are not. If a specific event precipitates failure in a patient who apparently has previously been adequately digitalized, more than 1.2 mg. of acetylstrophanthidin may be required to produce significant electrocardiographic changes. The one striking exception is myocardial

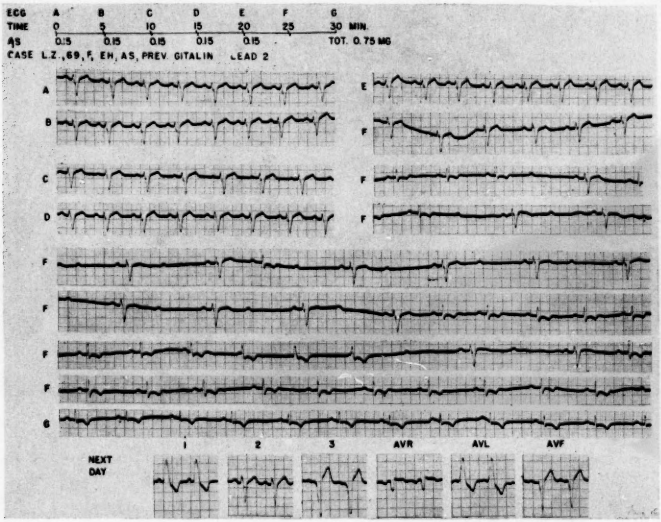

FIGURE 2. *Lead 2 in a Sixty-nine-Year-Old Woman with Aortic Stenosis Previously Digitalized with Gitalin. The control tracing shows sinus rhythm, with complete left-bundle-branch block and a rate of 80 per minute. After 0.6 mg., first-degree block occurred* (E). *Additional drug resulted in lengthening of the PR interval* (F), *2:1 block and complete heart block, with a return to normal of the QRS complexes* (F, *continuous tracing). Ten minutes after a total dose of 0.75 mg. the QRS complexes remained normal and first-degree block persisted. On the next day complete left-bundle-branch block and a prolonged PR interval were present.*

infarction, in which doses as small as 0.15 mg. may result in alarming changes in the electrocardiogram. In digitalized persons with persistent but static failure, small doses of acetylstrophanthidin may also produce striking changes in the electrocardiogram. It appears, therefore, that the clinical cause of failure may determine the dose of acetylstrophanthidin that is tolerated, regardless of the estimated amount of digitalis in the body.

Acetylstrophanthidin may cause nausea and vomiting. These manifestations rarely precede electrocardiographic changes. Additional acetylstrophanthidin accentuated these abnormalities. With nausea and vomiting, increased arrhythmia may occur for as long as thirty minutes after cessation of the drug. For these reasons, we regard nausea and vomiting as toxic reactions to acetylstrophanthidin and disagree with Lown and Levine, who recommend continued administration of the drug if only nausea and vomiting are present.[1]

Atrial premature beats were not produced by acetylstrophanthidin. Scherf and Schott[8] have emphasized the rarity of such beats after digitalis.

Ventricular premature beats were commonly produced, particularly in patients with atrial fibrillation, being uniform or multiform. Parasystole did not occur, and coupling was inconstant unless bigeminy was present. Digitalis-induced ventricular premature beats in man are said to have constant shape and coupling.[8] However, variability in shape[9] and in coupling[10] have also been reported. Ventricular bigeminal rhythms induced by digitalis or strophanthin in the laboratory animal are characterized by premature beats without constant shape or coupling and are regarded as due to increased automaticity rather than toxicity.[8] In our study, ventricular bigeminy was produced frequently. The ventricular premature beats were usually unidirectional, with constant coupling. Rarely, they were multiform, with inconstant coupling. Additional ventricular extrasystoles were not uncommon. All these reactions might be present in the same patient at variable times after a given dose of acetylstrophanthidin. Once bigeminy was produced, additional acetylstrophanthidin resulted in increased arrhythmia. For these reasons, we regard the appearance of ventricular extrasystoles as a toxic effect of the administration of acetylstrophanthidin.

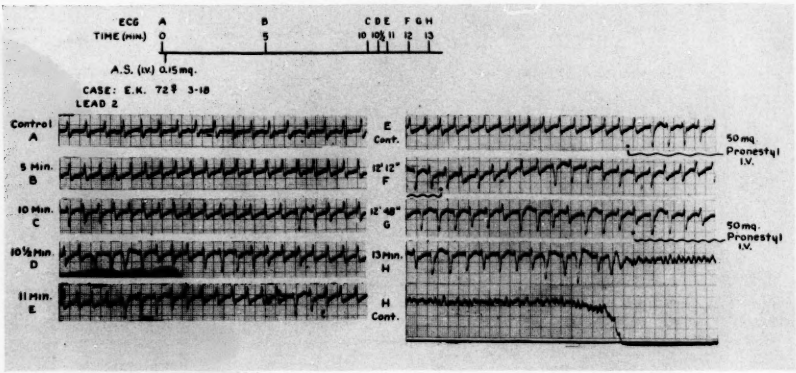

FIGURE 3. *Lead 2 in a Seventy-two-Year-Old Woman with Acute Myocardial Infarction Who Was Receiving Digitalis. The control tracing shows atrioventricular dissociation. P waves occurred irregularly, and the ventricular rate was regular at 170 per minute. The QRS interval was prolonged. Ten minutes after 0.15 mg., bidirectional ventricular tachycardia occurred* (C). *The administration of procaine amide was followed by ventricular fibrillation and death* (H).

Acetylstrophanthidin did not cause ventricular extrasystoles in persons without cardiac disease. Apparently, underlying heart disease is essential for their development.[11] Perhaps, for this reason, acetylstrophanthidin, as well as digitalis, is more likely to produce ventricular extrasystoles in patients with atrial fibrillation than in those with sinus rhythm. It is interesting that acetylstrophanthidin did not result in ventricular extrasystoles in a patient with a normal heart and profound electrolyte disturbances, in contrast to those with heart disease and similar electrolyte disturbances.[1]

Acetylstrophanthidin may produce all degrees of heart block. Block of any degree may appear initially with or without preceding ventricular extrasystoles. Additional acetylstrophanthidin changes the degree of block or provokes numerous ventricular extrasystoles, with or without a change in the degree of block. In 2 cases first-degree heart block lasted for twenty-four hours. These reactions are all manifestations of toxicity, for which we know no antidote.

Acetylstrophanthidin may abolish pre-existing bun-

dle-branch block or change its form. The changed form may be typical of block in the opposite bundle or may be indeterminate in character. These new forms of block may or may not alternate with the bundle-branch block present before the administration of acetylstrophanthidin. Rarely, third-degree heart block is associated with these changes. All the changes are manifestations of toxicity because additional acetylstrophanthidin increases the number of the administration of acetylstrophanthidin suggests that, in the absence of obvious toxicity, time and persistence of effects may be essential for such changes.

One death occurred in this study. The circumstances were similar to those in the case reported by Lown and Levine.[1] A small dose of acetylstrophanthidin in a very sick patient produced bidirectional ventricular tachycardia, for which procaine

TABLE 3. *Effect of Acetylstrophanthidin on Patients in Group 4.*

SUBJECT	AGE	SEX	DIAGNOSIS	RHYTHM & RATE		METHOD OF ADMINISTRATION	TOTAL DOSE	INITIAL TOXICITY		EFFECT OF ADDITIONAL ACETYLSTROPHANTHIDIN (IF GIVEN)	DURATION OF EFFECT
				CONTROL	FINAL			DOSE	MANIFESTATION		
	yr.						mg.	mg.			
H.F.	71	F	Aortic stenosis; enlarged heart.	Atrial fibrillation; irregular ventricular rate of 60/min.; left-bundle-branch block.	Atrial fibrillation; irregular ventricular rate of 88/min.; left-bundle-branch block.	0.15 mg. every 5 min.	0.3	0.15	2 ectopic beats; right-bundle-branch block.	Regular ventricular rate of 70/min.; right-bundle-branch block; increase in nausea at 10 min.	2 min.
J.E.	70	F	Aortic stenosis; enlarged heart.	Sinus rhythm; accelerated atrioventricular conduction; normal QRS complex; rate of 94/min.	Sinus rhythm with accelerated conduction & normal QRS complex; rate of 75/min.	0.3 mg. every 15 min.	1.2	0.6	Ventricular premature beat	Ventricular premature beats; bigeminy, predominantly unidirectional, with constant coupling; ectopic beats.	15 min.
L.N.	72	F	Aortic stenosis: enlarged heart.	Normal sinus rhythm; rate of 75/min.	Normal sinus rhythm; rate of 75/min.	0.15 mg. every 10 min. 8 every 5 min.	0.45	0.45	Complete heart block; increased nausea.	—	3 min.
D.H.	64	F	Aortic stenosis; enlarged heart; diabetes.	Normal sinus rhythm; rate of 80/min.	Sinus rhythm; rate of 77/min. (P-R interval prolonged).	0.15 mg. every 5 min.	1.05	0.45	Ventricular premature beats; bigeminy; multiform inconstant coupling; nausea & vomiting.	1st degree block; ventricular premature beat; ectopic beats; increasing nausea & vomiting.	10 min. (cardiac irregularity); <24 hr. (nausea & vomiting).
H.R.	64	F	Aortic stenosis: enlarged heart.	Normal sinus rhythm; rate of 80/min.	Normal sinus rhythm; rate of 72/min.	0.15 mg. every 5 min.	0.6	0.45	Nausea & vomiting	Increasing nausea & vomiting	<24 hr.

these new ventricular complexes, so that they quickly replace all the original ones and become rapid and regular.

Primary ST-segment and T-wave alterations did not occur. Minimal changes appear to be related to change in rate or rhythm. We have seen only 1 case in which the ST-segment and T-wave portion of the electrocardiogram was significantly altered. This occurred in a fifty-two-year-old man, not included in this study, who had pulmonary edema. A very large total dose of acetylstrophanthidin produced nausea, vomiting, first-degree block and subsequent ventricular tachycardia. Marked depression of the ST segment and decrease in the T wave occurred when first-degree block appeared. Enselberg, Altchek and Hellman[4] were likewise not impressed by any change in this portion of the electrocardiogram. No detectable change in the QT interval was observed. The absence of significant change in the ST segment after amide was given. Ventricular fibrillation and death resulted. Death could have been related to any or all of these factors. However, ventricular fibrillation and death after acetylstrophanthidin alone were reported by Enselberg, Croce and Lown[12] and also by Burrell and Coggins.[13] The administration of as little as 0.15 mg. of acetylstrophanthidin can cause severe toxic and at times uncontrollable reactions in patients who are on digitalis and have multiform ventricular premature beats, regularization of the ventricular response in atrial fibrillation, atrioventricular dissociation or ventricular tachycardia. Any of these arrhythmias may be produced by digitalis.[14,15]

It is because of the unpredictability of the toxic effects of extremely small doses of acetylstrophanthidin, particularly in patients who have previously received digitalis, and because of the inability of procaine amide or any agent at all times to control

them that we believe that both the use of acetylstrophanthidin and the acetylstrophanthidin tolerance test are dangerous.

None of the patients who had been given Digoxin to tolerance tolerated more than 0.6 mg. of acetylstrophanthidin. Indeed, toxicity appeared after as little as 0.15 mg., or 2.5 microgm. per kilogram of body weight. It is therefore still possible that digitalis intoxication is due to mobilization of edema fluid in digitalized patients, as suggested by Schnitker and Levine[16] and by Gouley and Soloff,[17] although potassium loss may be the principal or contributing factor.[1,18]

Summary and Conclusions

No electrocardiographic or systemic effect was observed in the normal person after the administration of 2.4 mg. of acetylstrophanthidin, which is twice the minimal digitalizing dose in patients with static cardiac disability.

The digitalizing dose is increased if a specific event, other than myocardial infarction, has precipitated failure.

The modification of the response to acetylstrophanthidin by a specific event precipitating failure is equally true for those previously receiving digitalis.

Significant responses of digitalized patients to acetylstrophanthidin in amounts up to 0.6 mg. are presumptive evidence of adequate or excessive digitalization.

Except for slowing of the ventricular rate in atrial fibrillation and rarely in sinus rhythm, significant electrocardiographic responses to acetylstrophanthidin are toxic.

Acetylstrophanthidin should never be used without electrocardiographic control because signs of toxicity may occur without symptoms and may not be recognized clinically.

Toxicity usually disappears within a few minutes but may persist for twenty-four hours.

There are no known antidotes capable at all times of abolishing the toxic effects of acetylstrophanthidin. Procaine amide, which is usually successful in abolishing some of the toxic arrhythmias produced by acetylstrophanthidin, may rarely cause ventricular fibrillation.

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NEEDLE BIOPSY OF THE THYROID GLAND*

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BOSTON

ALTHOUGH goiters are usually easily palpable and laboratory tests have become more helpful, the clinical diagnosis of thyroid disease is still often unreliable, and conclusive evidence of the nature of any particular goiter is frequently lacking. Surgery is often advised to settle the problem. The differential diagnosis of chronic thyroiditis, for instance, has always been a particularly fertile field of confusion. Marshall and Meissner[1] reported a correct preoperative diagnosis of only 17.5 per cent in 114 cases of Hashimoto's thyroiditis. Lindsay and his associates[2] found that only 20 per cent of the preoperative diagnoses of goiters, subsequently found to be thyroiditis, were correct. Since the medical management of many forms of thyroiditis has proved increasingly effective (through such agents as antibiotics, thyroid, cortisone and x-ray therapy), the indications for surgical intervention have, in many cases, narrowed down to merely a diagnostic procedure.

After the report of a series of successful thyroid needle biopsies at the Cleveland Clinic by Crile and Vickery,[3] this technic was adopted by the Thyroid

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Clinic of the Massachusetts General Hospital, and in the past four-year period, 175 needle-biopsy procedures have been performed. The biopsies have been done only on the recommendation of the Thyroid Clinic and not as a routine diagnostic measure.

Methods

Although this technic has been advocated as an office procedure,[3] we have elected to perform all our biopsies within the hospital so as to be better able to cope with any possible complication. So far, this precaution has proved unnecessary.

The Vim–Silverman needle has been used exclusively. The patient lies on a bed or on an examining table with a pillow under the shoulders, so that the neck is extended. The skin overlying the throat is prepared with alcohol, and a sterile towel is draped over the chest. The operator stands on the side opposite to the part of the thyroid gland that he wishes to biopsy. A skin wheal is made with 1 per cent procaine close to the mid-line, and the subcutaneous tissue infiltrated as well as the thyroid gland in the area to be biopsied. A total of about 2 ml. is used. A small incision is made in the skin through the wheal, and the trocar and sheath introduced with a rotary motion, tangential to the trachea toward the goiter. When it is thought that its point is resting against the thyroid gland, the trocar is removed, and the split needle placed in the sheath and inserted with firm pressure its full length into the substance of the gland. The needle is then held, and the sheath rotated until it has completely enclosed the needle, thus cutting free the tissue seized between the blades of the needle. Both needle and sheath are then rotated together a full turn, detaching the end of the core of gland, and then the sheath and needle are withdrawn together. It is well to apply immediate pressure to the biopsy area because a hematoma may otherwise develop. If a satisfactory biopsy has not been obtained and the field remains uncontaminated, further attempts may be made at this time. Pressure is maintained over the biopsy site for a period of three to five minutes, and the patient kept recumbent for fifteen minutes before final examination and discharge.

Table 1. *Analysis of 130 Needle Biopsies of the Thyroid Gland with Sufficient Tissue for Pathological Interpretation.*

Pathological Interpretation	No. of Cases	Percentage
Hashimoto's thyroiditis	25	19.2
Chronic thyroiditis, nonspecific	22	16.9
Multinodular goiter	22	16.9
No diagnostic abnormality recognized	19	14.6
Follicular adenoma	15	11.6
Hyperplasia	5	3.8
Carcinoma	5	3.8
Subacute thyroiditis	4	3.1
Riedel's struma	4	3.1
Fetal adenoma	4	3.1
Colloid nodule	4	3.1
Fibrosis	1	0.8

Complications

Although the introduction of a needle with a fairly large bore into tissue as vascular as thyroid was viewed with some alarm at the onset, complications have been very few. Three hematomas of considerable size developed, but neither respiration nor swallowing was compromised and it has never been necessary to explore the neck to control hemorrhage. There has been no sepsis.

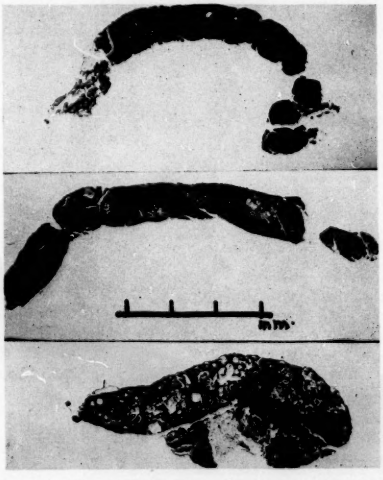

Figure 1. *Thyroid Needle-Biopsy Specimens at Low Magnification (Hematoxylin and Eosin Stain X9), Showing the Size of the Tissue on the Slides.*

The diagnoses of these biopsies were, from top to bottom, as follows: Hashimoto's thyroiditis; nonspecific chronic thyroiditis; and no diagnostic abnormality recognized.

Results

Needle biopsies were attempted on 175 patients, and sufficient tissue for histologic evaluation was obtained in 130 cases, or 74 per cent. The pathological interpretations of these biopsies are analyzed in Table 1. It is of interest that 55 diagnoses (42 per cent of the total) consisted of some form of thyroiditis, indicating the type of clinical goiter most commonly recommended for this procedure. Also of interest is the histologic interpretation of "nodular goiter" in 22 cases (17 per cent of all diagnoses), which was

the next most frequent diagnosis after "thyroiditis." As noted previously, the diagnosis of "chronic thyroiditis" versus that of "nodular goiter" has constituted the goiter problem that the Thyroid Clinic has considered perhaps most suitable for possible solution

FIGURE 2. *Survey View of a Needle-Biopsy Specimen of Hashimoto's Thyroiditis (Hematoxylin and Eosin Stain X40).*

This is a higher magnification of the biopsy shown in Figure 1. Note the typical lymphoid follicles and parenchymal atrophy.

by the needle-biopsy method; this is reflected in the relative frequency of these two entities in the biopsy series.

Figures 1 to 4 present photomicrographs of biopsy specimens of lesions of the various types under consideration.

On 1 occasion unsuspected cancer was diagnosed in a goiter. On 2 occasions, biopsies of questionable neoplasms (in which a surgical cure was highly improbable) have confirmed the presence of cancer more expeditiously than would have been possible with any other technic. In 3 patients metastases to the region of the thyroid gland from a remote primary source were demonstrated by needle biopsy.

DISCUSSION

Since the maximum size of specimen obtainable is about 2 cm. long and about 2 mm. in diameter, it is apparent that the pathologist must be prepared to offer an interpretation on a very small sample. This, of course, may be particularly difficult with thyroid tissue because of the frequently heterogenous distribution of its pathologic changes, unlike a needle biopsy specimen of the liver, which usually affords a fairly accurate reflection of the over-all histologic pattern of the entire organ. It is also important that the pathologist be informed of pertinent clinical data so that the microscopical observations can be best

FIGURE 3. *Thyroid Needle Biopsy of a Multinodular Goiter (Hematoxylin and Eosin Stain X32).*

Despite the small specimen, a nodular architecture is apparent.

evaluated in terms of that particular patient. For instance, although the objective microscopical findings may not be characteristically specific for any single diagnosis, it is often helpful if the pathologist can render an opinion that the biopsy is "consistent with" a particular diagnosis.

In 45 cases (or 25.7 per cent of all biopsy procedures), insufficient tissue was obtained for the pathologist to express any opinion. Progressive experience and skill in the biopsy technic has been reflected in a decreasing number of unsatisfactory

specimens. During 1952, the first year in which the procedure was used by us, 40 per cent of the total of 48 attempts failed to obtain sufficient tissue for diagnostic purposes. However, of the last 55 biopsy procedures (1954-1955), an inadequate specimen resulted in only 20 per cent of the cases. Biopsy failures have been attributable to several factors. Occasionally, a patient was so unco-operative or frightened that it seemed wise to desist from the attempt. On several occasions the only needle available was so dull that it would not safely pierce the goiter. However, we believe that failure is most frequently attributable to the underlying lesion. Hyperplastic glands may be so soft that the split needle enters the gland as though it were solid, but with the blades failing to grasp tissue between them.

FIGURE 4. *Subacute Thyroiditis, As Shown by Needle Biopsy (Hematoxylin and Eosin Stain X100). Three characteristic focal granulomas are visible.*

Multinodular goiter may contain such thin-walled cysts that unless the needle is tangential to the cysts, only tiny bits of wall may be obtained, and at times this appears to be normal thyroid tissue. Although the diagnosis of multinodular goiter has been made by needle biopsy more frequently than any diagnosis except thyroiditis, most of the failures of needle biopsy have been with this type of goiter. Conversely, fewer failures of a confirmatory needle-biopsy diagnosis have occurred in the cases in which thyroiditis was strongly suspected than with any other entity.

It should be emphasized that needle biopsy has been utilized only rarely in cases of "solitary thyroid nodules." Although these cases offer a never-ending problem of management, the histologic diagnosis of thyroid carcinoma is too frequently difficult enough when the pathologist has the entire "nodule" for study without risking such a decision on a minute specimen. Furthermore, we agree with Crile and Hazard[4] that this technic should rarely be used to confirm a suspected diagnosis of cancer, for in a curable lesion, cancer cells may be seeded along the needle tract. The goiter in thyroiditis is firm, diffuse and of exactly the right consistence to be grasped by the needle. After a little experience, the operator can predict the pathologic process with fair accuracy, by the feel of the needle as it is thrust through the gland. This has likewise been the experience of others.[4]

TABLE 2. *Comparison of Diagnoses during Two Consecutive Three-Year Periods.*

DIAGNOSIS	NO. OF CASES	
	1949-51*	1952-54†
Thyrotoxicosis	206	250
Multinodular goiter	297	277
Carcinoma	38	37
Thyroiditis, all forms	36	72
All others	197	129
Totals	774	765

*Pre-biopsy period.
†Includes 101 needle biopsies.

To determine whether or not this diagnostic aid had influenced the relative percentages of various diagnoses and in what manner, the total list of all diagnoses (clinical and pathological) made in the Thyroid Clinic for the three-year period (1949-1951) preceding needle biopsies was compared with a similar list for the three years (1952-1954) during which needle biopsy was employed in selected cases. Table 2 shows some of these figures. The periods are fairly comparable: 774 diagnoses were made in the first, and 765 in the second three-year period.

The most striking change was in the number of patients with some form of thyroiditis, which doubled in frequency in the second three-year period (Table 2). This increment is explained by the number (39) diagnosed by needle biopsy during that period. (Certainly, in many of these cases the diagnoses might eventually have been established at a later date, some of them at operation.)

SUMMARY

Needle biopsy of the thyroid gland has been employed at the Thyroid Clinic of the Massachusetts

General Hospital during the past four years. A total of 175 goiters have been biopsied, with aid in diagnosis in 74 per cent. Its greatest value has been in the diagnosis of thyroiditis.

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USE OF SERUM TRANSAMINASE LEVELS IN THE DIFFERENTIATION OF PULMONARY EMBOLISM AND MYOCARDIAL INFARCTION*

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THE diagnosis of pulmonary embolism continues to present a challenge to the clinician. Massive pulmonary embolism is often diagnosed correctly ante mortem and is identified with relative ease by the pathologist at autopsy. However, it is in nonfatal cases that the diagnosis is frequently missed or is in doubt. The correct diagnosis of nonfatal pulmonary embolism is of utmost importance because early recognition and treatment of thromboembolic disease and the correction of frequently present mild unrecognized congestive heart failure provide a means of prevention of fatal embolism, and, secondly, because when thromboembolism is overlooked, treatment may be inappropriately instituted for such conditions as myocardial infarction, tuberculosis, neoplasm and acute surgical emergency of the abdomen.

The diagnosis in many diseases can at present be established by specific laboratory tests, including x-ray and electrocardiographic examinations. Pulmonary embolism is one of the remaining conditions for which no specific diagnostic tests are available. It is perhaps for this reason that the diagnosis is so often missed. The diagnosis is a clinical one, depending on the correlation of nonspecific clinical and laboratory features integrated by a physician well aware of the many variations and the manifold clinical pictures that may be encountered. Nonfatal pulmonary embolism is more common than fatal embolism, but the ratio of diagnosis of nonfatal to fatal cases varies greatly.[1] Whereas in some hospitals this ratio is close to 1:1, in others, where the awareness of nonfatal embolism is great, the ratio is closer to 10:1.[2]

LaDue et al.[3-6] have recently introduced a new laboratory test, the determination of serum glutamic oxalacetic transaminase, a specific tissue enzyme concerned with the transfer of alpha-amino nitrogen of aspartic acid to alpha-ketoglutaric acid. This enzyme is encountered in all human tissues, but it is present in highest concentrations in heart and skeletal muscle, brain, liver and kidneys in descending order. The concentration of the enzyme in lung tissue, on the other hand, is low. Sudden necrosis of tissue, especially of heart muscle, is associated with an increased release of the enzyme into the blood stream and the finding of elevated serum concentrations. The original investigators reported on the value of this test in the diagnosis of myocardial infarction, liver disease and rheumatic carditis. Serum transaminase was consistently normal in a variety of inflammatory, degenerative, neoplastic, allergic and reactive disorders and thus helped to differentiate these conditions especially from myocardial infarction. The long list of conditions in which serum transaminase was tested and reported to be normal did not include pulmonary embolism.[6] Because this often mimics coronary occlusion and because it may be associated with the sudden necrosis of a large mass of tissue, it appeared important to determine whether pulmonary embolism is associated with elevated serum transaminase. If elevated, the test would not be helpful in differentiating myocardial from pulmonary infarction but could help distinguish pulmonary embolism from inflammatory and neoplastic conditions; if within normal limits, it could be an additional aid in the differential diagnosis of pulmonary embolism and myocardial infarction.

Materials and Methods

During the months of September and October, 1955, the diagnosis of nonfatal pulmonary embolism was made in 12 patients admitted to the Graduate Hospital of the University of Pennsylvania. The diagnosis was based on clinical findings and electrocardiographic and roentgenologic changes (Table 1). The pertinent clinical data obtained from the 12 patients are summarized in Table 1. The clinical pictures were diverse, varying from nearly fatal embolism with profound shock to transient pleuritic chest pains in

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patients with known thrombophlebitis. The serum of these patients was analyzed repeatedly for transaminase content. The first determination was always made within forty-eight hours, and usually within twenty-four hours, of the embolic episode. Repeat determinations were carried out up to nine days after the embolism. Serum glutamic oxalacetic transaminase was determined according to the method of Karmen, Wróblewski and LaDue.[5] Normal values with this method range between 10 and 40 units per milliliter of serum. A number of normal subjects and patients with unrelated diseases, including postoperative patients without thromboembolic complications, were tested and found to have normal serum transaminase levels. Patients with proved diagnoses of myocardial infarction consistently manifested values above this level during the first several days after infarction. This is in close agreement with the findings of LaDue and Wróblewski.[6]

TABLE 1. *Important Clinical Data in 12 Consecutive Patients with Nonfatal Embolism.*

CASE NO.	PRIMARY DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	SHOCK	ELECTROCARDIOGRAPHIC CHANGES	X-RAY EVIDENCE OF PULMONARY EMBOLISM	HIGHEST TRANSAMINASE VALUE	COMMENT
						units/ml.	
1	Aneurysm of abdominal aorta; postoperative pulmonary embolism.	Myocardial infarction	Present	Ischemic pattern	Hazy right sulcus	37.5	Transaminase helpful in diagnosis
2	Thrombophlebitis, with pulmonary emboli	Liver disease	Present	Right-axis deviation (transient ischemia)	Inconclusive	78.3	Jaundice believed due to multiple pulmonary emboli
3	Pulmonary embolism after hysterectomy	Myocardial infarction	Present	Ischemic pattern	Linear strands	20.5	Transaminase helpful in diagnosis
4	Thrombophlebitis, with pulmonary embolism	None	Absent	None	None obtained	15.5	
5	Congestive heart failure, with bloody effusion	Neoplasm; tuberculosis.	Absent	Right-axis deviation	Left-sided effusion	35.5	Fluid negative for acid-fast bacilli & malignant cells
6	Pulmonary embolism	Acute abdominal emergency	Absent	Inverted T wave in Lead 3	Haziness; linear strands.	34.0	Negative laparotomy
7	Pulmonary embolism after hysterectomy	Myocardial infarction	Present	Ischemic changes	Elevated diaphragm; haziness; linear densities.	41.5	Transaminase helpful in diagnosis
8	Thrombophlebitis, with pulmonary embolism	Myocardial infarction	Absent	Transient minor changes	Platelike atelectasis	24.0	Transaminase helpful in diagnosis
9	Pulmonary embolism; paroxysmal atrial tachycardia.	Myocardial infarction	Absent	Transient axis changes	Small effusion	12.5	Transaminase helpful in diagnosis
10	Pulmonary embolism	Myocardial infarction	Absent	Q wave & inverted T wave in Lead 3 for 1 day	Wedge-shaped infarct	37.0	Transaminase helpful in diagnosis
11	Thrombophlebitis, with pulmonary embolism	Myocardial infarction	Absent	—*	Not taken	28.0	—
12	Pulmonary embolism	Myocardial infarction	Present	Ischemic changes	Large infarct	26.5	Transaminase helpful in diagnosis

*No tracing taken.

RESULTS

The results of the transaminase determinations are plotted in Figure 1. The highest concentration of serum transaminase found at any time in each of the patients is shown in Table 1. Consistently normal values were found in 11 of the 12 patients. One patient (Case 7) had a borderline elevation (41.5 units per milliliter) on the fifth day, but determinations on the first and third days after the embolic episode were normal. Another patient (Case 2) had definitely elevated transaminase levels on the first and third days (51 and 78 units per milliliter, respectively); this patient also had obstructive jaundice, with a total serum bilirubin concentration of 2 mg. per 100 ml. and a bromsulfalein retention of thirty-eight per cent in 45 minutes. Wróblewski and LaDue[6] have reported elevated transaminase levels in obstructive, as well as parenchymal, jaundice. It is therefore believed that the elevation of the transaminase level observed in Case 2 was related to the presence of jaundice and not to the pulmonary embolism directly.

It should be emphasized that the diagnosis of pulmonary embolism was made without knowledge of the transaminase level in all patients. However, in 7 of the 8 patients in whom myocardial infarction was the main differential diagnosis, the finding of normal serum transaminase levels was in retrospect considered to support the diagnosis of pulmonary embolism (Table 1).

Discussion

Although pulmonary embolism may present a most variable picture and may be confused with a variety of clinical conditions, differentiation is perhaps most frequently necessary from myocardial infarction. In the present series 8 of 12 patients presented this problem. Myocardial infarction is almost invariably associated with elevation of serum transaminase levels, since, in the experience of LaDue and Wróblewski,[7] 297 of 300 patients with myocardial infarction manifested this elevation. Furthermore, these authors found the degree of elevation to be proportional to the extent of destruction of myocardial muscle.[4] Therefore, a

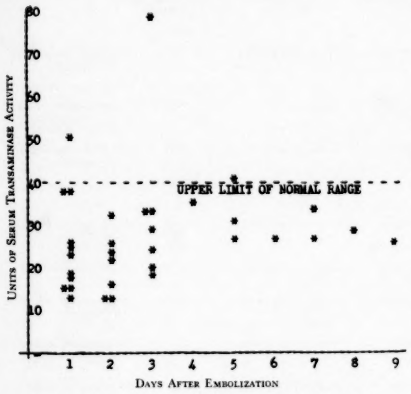

Figure 1. *Transaminase Levels in Patients with Pulmonary Emboli.*

myocardial infarction extensive enough to result in a decreased cardiac output and clinical shock certainly should be accompanied by marked elevation of the level of serum transaminase. On the other hand, shock produced by pulmonary embolism, as encountered in 5 of our patients, was not associated with elevation of serum transaminase except in the patient who was jaundiced. Thus, the determination of the serum transaminase appears to be a valuable supplement to the electrocardiogram, which is frequently equivocal and open to diverse interpretations in such cases.

The classic electrocardiographic pattern of acute cor pulmonale originally described in pulmonary embolism by McGinn and White[8] is found in only a few patients.[9] Dack and his associates[10] have stressed the frequency of an electrocardiographic pattern of coronary insufficiency encountered in pulmonary embolism. The majority of their patients over fifty years of age with pulmonary embolism manifested this pattern, which consisted chiefly of depressed R-ST segments and inverted T waves in one or more leads. This pattern is identical with that frequently seen in shock and myocardial ischemia of any cause and, if it persists for more than twenty-four hours, suggests subendocardial necrosis. However, the persistence of this pattern for days and weeks after pulmonary embolism in the apparent absence of subendocardial infarction has been reported.[11] Whether in such cases pulmonary embolism and shock actually result in subendocardial infarction has remained a matter of dispute that in the individual case can only be solved by autopsy. The determination of the serum transaminase level may prove to be a decisive means of separating patients in whom massive pulmonary embolism and shock have resulted in actual subendocardial necrosis from those in whom transient subendocardial ischemia did not progress to necrosis. In the several cases reported here in which profound shock followed pulmonary embolism, subendocardial infarction apparently did not ensue.

The failure of serum transaminase levels to rise after pulmonary embolism, uncomplicated by conditions that by themselves can cause elevations in serum transaminase levels, may be explained on several bases. In the first place, the concentration of transaminase in lung tissue is exceptionally low — about a fiftieth of the concentration found in myocardial tissue.[7] Secondly, pulmonary embolism may occur without infarction. And, finally, the densities that are demonstrable on the x-ray film after an embolism are not indicative of the amount of tissue necrosis that has occurred. Extravasation of blood, bronchial obstruction and atelectasis, splinting of both leaves of the diaphragm and effusion all contribute to the production of these densities.

The exclusion of myocardial infarction, alone or in association with pulmonary embolism, may be of considerable practical value. Although the immediate treatment of massive pulmonary embolism is virtually identical with that of myocardial infarction, the long-term management is quite different. Whereas the patient with a myocardial infarction should remain in physical and mental repose for weeks or months, the patient with thromboembolic disease should have energetic anticoagulant treatment and ambulation as soon as the acute thrombosis is controlled. The patient does not have to be protected from emotional stimuli, and necessary diagnostic tests can be carried out sooner. The period of convalescence and of hospitalization may be considerably shortened when one can safely exclude myocardial infarction. On the other hand, when thromboembolic disease is diagnosed, anticoagulants may be required for prolonged periods, especially in patients with recurrent episodes. If there is associated congestive heart failure, digitalization should be instituted rapidly in the patient with pulmonary embolism, but cautiously in patients with myocardial infarction because of the known danger of ectopic rhythms.

An example of the difficulties that may be en-

countered in differentiating myocardial and pulmonary infarction, and the assistance that transaminase levels may provide, is afforded by the following case*:

H.C., a 63-year-old Negress, was first admitted to the Graduate Hospital of the University of Pennsylvania on July 26, 1955, with complaints of cough, weakness and anorexia of several weeks' duration. During the previous 3 weeks she also experienced increasing exertional dyspnea and anginal pains.

Her medical and family histories and a review of the systems were noncontributory. The patient denied any long-sustained chest pains.

Physical examination showed a well developed and well nourished woman who appeared tired and somewhat confused. There was a Grade 2 hypertensive retinopathy; examination of the chest revealed diminished breath sounds over the middle portion of the right lung, but no rales were heard. The heart appeared slightly enlarged, and a basal systolic murmur (Grade 2) was heard. The remainder of the examination was negative.

The temperature was normal, the pulse 90, and the respirations 25 to 35. The blood pressure was 160/100.

Examination of the blood disclosed a red-cell count of 3,600,000, with a hemoglobin of 10.2 gm. per 100 ml., and a white-cell count of 9800, with 75 per cent neutrophils. The sedimentation rate was 40 mm. (corrected) per hour. Urinalysis was negative. Blood chemical determinations, including sugar, urea and liver-function tests, were all within normal limits except for a slightly elevated zinc turbidity of 14 units.

A roentgenogram of the chest demonstrated a large density in the right-upper-lung field that at first was thought to represent a neoplastic process. Bronchoscopy gave no evidence of neoplasm by direct inspection or by examination of bronchial secretions. An electrocardiogram obtained on the day after admission showed a deep Q wave in Lead 3, a Q wave of lesser depth in Lead aVF and T-wave inversion in the precordial leads on the right. These findings were suggestive of a posteroseptal infarction, possibly in an acute phase. All further diagnostic tests were temporarily discontinued, and the patient was treated with strict rest. In the course of the next 6 weeks repeated electrocardiograms revealed only minor changes, and the question was raised whether the changes were due to an old myocardial infarction or pulmonary infarction or both. Unfortunately, at the time of the 1st admission, the transaminase test was not available. Serial chest films showed a gradual resolution of the lung density previously described, with the persistence of a well outlined oval residual mass in the right upper lobe and with several smaller linear densities in both lungs. The roentgenographic findings and the clinical course led to a final diagnosis of pulmonary infarction. The patient became asymptomatic and was discharged on September 22.

She was readmitted to the hospital on October 11 with marked dyspnea and anxiety. The heart rate was 120, with frequent ventricular extrasystoles not previously observed. The respiratory rate was 40. The lungs were clear except for faint inspiratory rales heard over both bases posteriorly. An electrocardiogram was immediately obtained but showed no changes since the tracing obtained 3 weeks earlier. Another electrocardiogram on the following day was identical in appearance. It was thought that the patient had suffered another pulmonary embolism. However, a roentgenogram of the chest on the next day, as well as another film obtained 2 weeks later, revealed no fresh pulmonary abnormalities. Serial transaminase determinations were ordered on admission. There was a significant elevation of the serum level on the 1st day (82.5 units per milliliter), with a gradual return to normal in 3 days. Another electrocardiogram obtained after the report of the elevated transaminase disclosed definite changes consistent with, but not pathognomonic of, a new nontransmural infarction. In the absence of any radiologic evidence of new pulmonary emboli the finding of a markedly elevated serum transaminase level was thought to establish the diagnosis of a myocardial infarction in this case. The patient was treated for a coronary occlusion by means of rest and anticoagulants; she was digitalized and was discharged for further rest at home on November 3.

*Serum transaminase levels determined in an additional 14 patients with pulmonary embolism were consistently normal in 10. Elevation on one or more determinations was noted in 4 patients. In each case an associated condition known to cause a rise in serum transaminase was present: liver necrosis, portal cirrhosis, extensive third-degree burns and fracture of the femur, with skeletal-muscle injury.

Summary and Conclusions

Serum glutamic oxalacetic transaminase levels determined repeatedly in 12 patients with pulmonary embolism were normal in 11. One patient in whom the transaminase was elevated had jaundice (in which high levels of transaminase are usually encountered).

Uncomplicated pulmonary embolism is not associated with increased serum transaminase levels.

The determination of serum transaminase levels is suggested as an additional aid in the differentiation of pulmonary embolism and myocardial infarction.

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MEDICAL PROGRESS

THE MENOPAUSE (Concluded)*

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MANAGEMENT

One of the primary responsibilities of the physician is to determine that the symptoms are actually related to the menopause and not due to some underlying nonrelated disease. Symptoms associated with anxiety and depression can mimic or mask other conditions, and it is tragic for both patient and physician if all complaints arising at this time of life are casually assumed to be due to the menopause. Once it is established that the symptoms are indeed menopausal, the physician has an unequalled opportunity to serve his patient by offering a rational explanation of the events occurring. By indicating his willingness to listen, he can do much to reassure his patient concerning her fears and apprehensions. Most depressions occurring at this time can be well handled by the family physician by the simple process of interviews in which the patient has an opportunity to discuss her symptoms and her problems. It should again be emphasized that estrogen does not appear to affect the psychologic component of the menopause other than by its psychotherapeutic action.[11,116] It is also probable that in this as in other clinical situations, the relief of somatic symptoms helps alleviate psychogenic complaints.

Estrogens

Although marked relief from hot flashes may be obtained by simple reassurance, sedation or placebos,[117] the accepted treatment of hot flashes, which may be troublesome and embarrassing, is the proper administration of estrogens. It is difficult to assess what portion of the beneficial effect of estrogen is due to its physiologic effect and what is due to the psychotherapeutic effect. The indiscriminate and injudicious use of estrogens is to be condemned. Weaver[118] reported that of 2200 women admitted to the Neuropsychiatric Service of the University of Texas Hospital, 1670 had received estrogens without benefit. The medication was given to those under twenty-five for "weak ovaries" or over twenty-five for "an early or late change." Israel[119] has stated, "It's about time we spend more time mitigating menopausal anxiety and less time prescribing estrogens as an 'all purpose female tonic.'"

Opinion about the need for estrogens at the time of the menopause varies widely. It is certainly true that the majority of women passing through the menopause are not sufficiently disturbed by hot flashes to require any therapy. In others, the symptoms are such as to warrant treatment. There is opposition to the use of estrogens on the basis both that the menopause is a normal event and should not be interfered with and that the administration of estrogen will postpone the eventual physiologic adjustment.[8,120] The possible carcinogenic effect of estrogens has led to warnings against their use. There is no general agreement that estrogens delay a physiologic adjustment or that, if they do, it is necessarily deleterious.[37] It has frequently been the custom to administer estrogens for short periods, the patient being gradually weaned from medication as hot flashes became less severe or less frequent.

If estrogens are elected as treatment, small doses of an oral preparation will usually relieve the hot flashes. However, when estrogens are used, they must be given by a definite schedule with periodic interruptions so that if withdrawal bleeding does occur, its mechanism will be reasonably certain. In this clinic, as elsewhere, it is the custom to give estrogens for thirty days, to stop for seven days and then to resume. Bleeding occurring during the seven days when medication has been stopped can reasonably be ascribed to the estrogen administered rather than to an unrecognized uterine carcinoma. The need for periodic interruption of estrogen therapy has been repeatedly stressed; yet it is common to see patients with the complaint of postmenopausal bleeding who on questioning are found to be taking an estrogen pill daily without interruption or have been receiving weekly injections for a long time. Such patients require dilatation and curettage to exclude possible intrauterine carcinoma, and yet the necessity for the curettage could have been eliminated by proper scheduling of therapy. Rarely should estrogens be given to menopausal patients who are still having periods.

There is a large literature concerning the various preparations of estrogens and the several routes of administration. There was early enthusiasm for the subcutaneous implantation of estrogen-containing pellets,[121] but this technic has not been in wide general use. Some[122-124] favor pellet implantation at the time of oöphorectomy, believing that the symptoms of sudden loss of ovarian function are best alleviated in this way. Such procedures are not necessary when medication can easily be given by mouth. There is ample evidence that there is little difference in clini-

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cal effect between the synthetic compounds and those of natural origin[125-127] although the studies of Kupperman et al.[128] suggest that ethyl estradiol is slightly more effective than the stilbene derivatives. It is advisable for the physician to acquaint himself with one or two preparations rather than to try various estrogens with which he is not familiar. It is claimed that some synthetic preparations more recently produced are less likely to cause withdrawal bleeding,[129] but it is probable that they are less active estrogens. Sevringhaus[130] has reviewed the problems of therapy. In the last three years there have been reports on the use of chlorotrianisene,[131,132] which can be taken orally and which is stored in body fat with a slow release.

Those who prefer not to use estrogen or do not find it necessary for the relief of menopausal symptoms have no great points of disagreement with those who prefer short courses of estrogen over a period of a year or two when the symptoms are most intense. The arguments about prolongation of the menopause and carcinogenicity of estrogens are less cogent when short-term therapy is concerned. The larger problem relates to the prolonged use of estrogens in an attempt to modify or at least to delay the atrophic changes in the skin, genital tract, bone and cardiovascular system of the postmenopausal woman. Should not perhaps all women at the menopause receive estrogens for the rest of their lives? There are attractive arguments to favor such a thesis. Within the last fifty years, the average life expectancy of women has increased from forty-eight and seven tenths years to seventy-two and four tenths years[87] so that the average woman now faces an increasing number of postmenopausal years. It is not unreasonable to suggest that perhaps atrophic changes in the genital tract, dermal atrophy and atherosclerosis and, most important of all, osteoporosis are preventable disorders. There is even some evidence that estrogen in aged women improves intellectual function.[133] Stoddard,[134] in a recent review, discussed the problem of the postmenopause and stressed the increasing importance of this time of life.

Opponents to the thesis of prolonged estrogenization postmenopausally raise the issues of prolongation of the period of normal physiologic adjustment and of tampering with natural processes. As Shelton[37] has pointed out, women themselves "want to know what is wrong with having this objective evidence of deterioration in the sixties or even seventies instead of in the forties, if one is destined to live an additional 20 or 30 years." So far as tampering with nature is concerned, Shelton states:

> The final argument that the menopause is a natural phenomenon and should not be tampered with, is to me the most vapid of all. It is reminiscent of the outworn arguments against anesthesia in childbirth, against cosmetics, against everything progressive in life. When I was a young man, any woman who used cosmetics or smoked cigarettes was a bad woman. Proper ladies fainted at the word "sex." The female anatomy was effectively, if atrociously, hidden from the roving eye of the male. People died by the hundreds of typhoid, of smallpox and of diphtheria. We no longer live in that day of the survival of the fittest. The very person who argues that the menopause is a natural phenomenon fights nature every day. He pasteurizes his milk, boils his instruments, vaccinates his stock and his children, sprays and buds his fruit trees, flies against gravity, makes new elements and splits the atom. Is the menopause any different? During the past 50 years women have overcome the prejudice against cosmetics, political equality and freedom of dress. I am convinced that as they grow older, anything which keeps them looking, feeling and acting young will be employed with or without the sanction of the medical profession. Phenobarbital, anticholinergic drugs, and psychotherapy, advocated by so many, may help to alleviate the hot flushes and the panic reactions incident to the menopause, but they will not postpone the aging process. Estrogen will.

Overenthusiasm for postponement or alleviation of the aging process by steroid administration should be tempered by the realization that no proof yet exists that such an effect can be produced. Objective evidence is needed to answer the question whether aging progresses more rapidly in the absence of sex-specific steroids. As Pincus et al.[135] have stated, "when we consider possible specific effects of the steroids in aged persons, we are confronted with the unknown."

The chief opposition to the prolonged use of estrogens is related to the question, still unsettled, whether estrogens are carcinogenic agents in human beings. In mice, estrogens can produce cancer, and the frequency of mammary cancer in male mice has been shown to vary directly with the amount of estrogen injected and the duration of treatment.[136] Loeb[137] has demonstrated that in mice with a high frequency of cancer, the rate of mammary cancer could be reduced to almost 0 if the ovaries were extirpated at the time of early sexual maturity. In animals spayed at five or six months, the cancer rate was lowered but not to such an extent as when the ovaries were removed earlier.

Although, in human beings, direct evidence is lacking, there are several observations to suggest a carcinogenic effect of estrogen. In 1936, Novak and Yui[138] pointed out the frequent coexistence of endometrial carcinoma and hyperplasia and described 104 patients with adenocarcinoma of the endometrium of whom 25 had coexisting hyperplasia. Jones and Brewer[139] challenged the significance of this finding on the basis of their observation that in patients with endometrial carcinoma, the ovaries may function normally, and that the uninvolved portion of the endometrium may be normal and respond normally to ovarian stimulation. Other observers,[140-142] however, agree that hyperestrogenism, as reflected by endometrial hyperplasia, is a factor in the genesis of endometrial carcinoma. Novak[143] has recently reviewed the problem of endometrial hyperplasia and concludes that although exogenous estrogen can produce microscopical patterns indistinguishable from early endometrial carcinoma and estrogens can cause hyperplasia, it is still unjustified to conclude that

estrogens definitely cause adenocarcinoma of the uterus.

In a large series of patients with granulosa-cell tumors, which are commonly accepted as estrogen-producing lesions, 67 per cent had an associated proliferative endometrium. Of 38 postmenopausal patients with such tumors, 8 showed endometrial carcinoma, and in 3 of the 8, there were also carcinomas of the breast.[144] Ingraham et al.[145] have also commented on this relation. These statistics suggest that about 15 per cent of feminizing tumors are associated with endometrial carcinomas. Emge,[146] however, in a survey of material from numerous institutions throughout the United States, showed that the incidence was more likely to be about 3.3 per cent, which is close to the predictable incidence occurring by chance.

The association of prolonged estrogen activity with fundal carcinoma is further suggested by the observations of Crossen and Crossen,[147] who found that of 30 cases of cancer of the uterine fundus, the menopause occurred at the age of fifty years or later in 22 and who concluded that when the menopause is delayed to the age of fifty or more, it is an indication of aberrant endometrial activity and a warning of a tendency to endometrial carcinoma. More recently, Randall[86] again called attention to the significance of the delayed menopause, demonstrating that over 35 per cent of a series of women with adenocarcinoma had periods to the age of fifty-one or more; he commented on the absence of adenocarcinoma of the fundus in women whose vulval and vaginal tissues suggested deprivation of estrogenic hormone. It has been reported that about five times as many women with breast cancer have a late menopause as normal women,[148] and it was even suggested that women menstruating beyond the age of forty-eight or fifty years should have a prophylactic artificial menopause.

There is also evidence that ovarian stromal hyperplasia, which is usually accepted as evidence of ovarian activity and a possible source of estrogen, is associated in a statistically significant manner with carcinoma of the fundus and breast. Woll et al.,[149] and later Novak and Mohler,[150] showed an increased frequency of stromal hyperplasia in patients with fundal carcinoma; Sommers and Teloh[151] demonstrated an increased frequency in patients with carcinoma of the breast. Engle[15] has pointed out, however, that there is no direct evidence that the ovary showing stromal hyperplasia is producing estrogen.

Several authors have reported cases in which prolonged estrogen administration has coincided with the development of uterine[141,142,152] or breast carcinoma.[138-140,153-155] Admittedly, such cases do not prove that estrogens are carcinogenic in human beings, and yet such observations in light of the previously discussed evidence cannot be lightly dismissed. On the other hand, it is frequently stated that if estrogens are carcinogenic, one would expect to see more striking evidence of the fact, in view of the large numbers of women who have taken estrogens for years, and it has been questioned whether the therapeutic doses of estrogen commonly used could be carcinogenic.[156] It has been pointed out that 700 kg. of estrogens are manufactured in or imported into the United States each year; yet there was no change in the incidence of cancer of breast and sex organs in 1950 from that in 1930, when estrogens were rarely used. The death rate from these causes was essentially the same in both years.[37]

The reader of the papers referred to above, taken singly or as a group, becomes impressed with what seems to be a significant association between hyperestrogenism and uterine and mammary carcinoma. Larson[157] recently analyzed the problem critically, referring to two impersonal biases that affect numerical values: the histologic bias, which is "the unintentional selection of histologic specimens with the most unusual disease, since special effort is made to procure and save those because of their interest"; and the hospital bias, which is "the unintentional selection of certain types of disease by a hospital because physicians in that hospital are known to be especially competent or interested in them." Larson pointed out the wide discrepancy of views concerning the relation of hyperplasia and endometrial carcinoma and concluded that there is no large series to show that the coexistence of these two entities is any greater than could be expected on the basis of chance. In a reevaluation of the statistical evidence of the association of endometrial carcinoma and feminizing tumors, he found the association too frequent to be due to chance, and although this represents a strong argument for the carcinogenic action of estrogen in the breast, he presents evidence that the coexistence of feminizing tumors may be a manifestation of the high incidence of multiple lesions seen in many cases of cancer. Larson also reviewed the significance of the delayed menopause and produced evidence that the average age of the menopause in women is forty-nine years instead of forty-seven years and that women with endometrial carcinoma do not have a later menopause than a control group. Backman[158] has also shown that the menopause is occurring at progressively later ages in all women. The menopause probably began in ancient times at about the age of forty, in the period 1500-1830 at about the age of forty-five and nowadays at about forty-eight years of age. Larson criticized the evidence of association of ovarian stromal hyperplasia and endometrial carcinoma on the basis that the control groups of Woll et al. were not true controls. Regarding Randall's[86] statement that abnormal bleeding at the menopause is associated with a higher incidence of postmenopausal endometrial carcinoma, Larson claimed that Randall's conclusion is erroneous and that the correct conclusion from such data is that a woman

with postmenopausal bleeding is two and a half times as likely to have a history of premenopausal bleeding as a woman without postmenopausal bleeding. He concludes: "there is but meager evidence to implicate estrogens in the etiology of endometrial carcinoma."

It seems reasonable, then, to state that the concern over the use of estrogens[140,142,159] does not seem justified by a review of the available evidence. There remains no direct proof that estrogens are carcinogenic when used therapeutically, and the circumstantial evidence has been seriously challenged by Larson's work. A large series of patients observed for a long time are needed to determine whether the possible advantages of long-term estrogen therapy in mitigating the onset of genital atrophy, osteoporosis and cardiovascular change outweigh the seemingly slight risk of producing endometrial or breast carcinomas. Estrogen therapy is, in the present state of knowledge, thought to be contraindicated in patients with a history of mammary or uterine carcinoma or a family history of such a tumor.[144] Yet the caution in this problem is motivated by the fear of legal rather than medical complications.

Androgens

If one elects to use estrogen therapy, one must also decide whether or not to supplement treatment with androgens. In the last two decades, the use of androgens alone or more commonly in combination with estrogens has been advocated in the management of menopausal symptoms. In 1937, Salmon[160] showed that testosterone in large doses could suppress the urinary excretion of gonadotrophic hormone and have a full estrogenic effect on the vaginal smear. Symptoms were relieved after 400 mg. of testosterone propionate had been administered. Numerous papers appeared confirming the beneficial effect of androgens on menopausal symptoms[161,162] and establishing their clinical use largely on an empirical basis. The early rationale offered was their suppression of gonadotrophic production by the pituitary gland,[160,163] but it soon became evident that the beneficial effects could not be explained so simply when it was observed that relief of symptoms could be obtained by doses of androgen too small to suppress pituitary gonadotrophins. Although Salmon's[160] original work suggested an estrogenic effect on the endometrium, subsequent observations indicated that it produced an atrophic vaginal smear and an atrophic endometrium.[163-165] The observation[166] that testosterone in large doses has an estrogenic effect whereas in small doses it has an atrophic effect on the endometrium explained the earlier discrepancy on reports of its action. More recently, it has been observed that the hypoplasia induced by testosterone is preceded by an initial progesteronelike stimulation.

The action of testosterone in relation to estrogen is complex, and the apparent estrogen antagonistic effect may be mediated through a direct peripheral action, a direct effect on the ovary, by suppression of the pituitary gland or by a combination of all three actions. Salmon[166] reviewed the rationale for the use of androgens and raised the question whether in some women there might not be an androgen deficiency. Studies of steroid excretion[17,135] do indicate a decline in androgen output in aging women as well as men. The observations of Kenyon et al.,[167] Kochakian and Murlin[168-170] and others on the protein anabolic effect of androgens lent further support to their clinical use and provided a reasonable explanation for the improved sense of well-being experienced by patients receiving androgens.

Although there was initial enthusiasm for the use of androgen therapy alone, it soon became apparent that a combination of estrogen and androgen was more effective in the control of menopausal symptoms, and numerous articles have appeared in support of combined therapy.[171-176] The advantages are a synergistic effect on pituitary suppression, and the protein anabolic effect of androgen that presumably results in a sense of well-being and an increase in libido. In addition, the use of androgens permits a smaller dose of estrogen and decreases estrogen-induced bleeding. Good effects are reported to be obtained by a combination of diethylstilbestrol and methyltestosterone in a ratio of 1:20.[177]

In a controlled study of a comparison of the effects of estrogen alone, a combination of estrogen and androgen and androgen alone and a placebo, the combined therapy was found most effective.[178] Combined therapy seems particularly indicated, then, in women with osteoporosis[115] and in those in whom estrogen-induced bleeding is a problem, as well as in women with chronic cystic mastitis associated with the menopause. Although it is generally held that the menopause does not occur until periods cease, there are women who have distressing menopausal symptoms in spite of the fact that they menstruate regularly. These women, according to Salmon,[166] are helped by testosterone. In contrast to estrogens, testosterone appears to have a beneficial effect on mental depression.[179] The effect of androgens on urinary-tract symptoms has been previously commented on.[36,39]

The numerous preparations and dosages of the androgens have been reviewed by Salmon.[180] If one is to avoid unpleasant masculinizing effects, the total dose of testosterone propionate or its equivalent given parenterally must be less than 300 mg. a month. It is reported that some of the complications of androgen can be avoided by the use of methylandrostenediol, whose masculinizing action is supposedly less than that of testosterone.[181] It can be questioned, however, whether the assumed lack of masculinizing effect of methylandrostenediol is not merely due to its being less potent than testosterone.

The use of androgens has recently been thoroughly reviewed by Friedenberg.[182]

Not all are agreed that androgens should be used in the treatment of the menopause,[183] and it does seem that the majority of women who need hormonal therapy can be satisfactorily managed with estrogen alone. Testosterone is no substitute for estrogens.

Menopausal and Postmenopausal Bleeding

A difficult problem occurs when the woman undergoing the menopause experiences abnormal uterine bleeding because it involves the decision between immediate curettage or a policy of watchful waiting to see what subsequent periods will be like. On the other hand, the management of postmenopausal bleeding, which is defined as bleeding occurring after cessation of menstruation for a year, is less of a problem because it requires prompt curettage.

Abnormal vaginal bleeding is so frequent at the menopause that some sort of general plan is necessary if one is to avoid a large number of unnecessary uterine curettages. When one is confronted by a patient complaining of one episode of abnormal bleeding, prolongation of a period, an excessively heavy period or one episode of spotting, it is probably safe to wait for another cycle if the complete examination is negative and cytologic smears of the cervix and vagina are normal. A second abnormal episode is generally accepted as an indication for curettage. Many patients and physicians prefer the reassurance of a negative curettage to the frequent visits and examinations that the watchful-waiting policy demands. It hardly seems necessary to warn that attempts at hormonal control of menopausal bleeding should not be made until cancer has been excluded. Improper administration of estrogens can make decisions about proper management even more difficult.

Very rarely menstruation can resume after the menopause. There are isolated reports[184] of pregnancy after the menopause although it must be questioned whether these cases do not occur in women who have experienced merely amenorrhea rather than true menopause. Occasionally, a patient with postmenopausal bleeding will be found to be bleeding from a secretory endometrium, indicating previous ovulation.[85,185] One of the more common causes of postmenopausal bleeding is carcinoma of the reproductive tract. In 1000 cases studied by Sutherland and McBride,[185] the rate was 27.8 per cent and a similar figure was reported by Brewer and Miller.[186] In the latter series, benign lesions accounted for 34.1 per cent of uterine bleeding, and in 38.4 per cent, no cause was demonstrated. The reported frequency, however, of nearly 30 per cent makes thorough examination and curettage mandatory in the management of postmenopausal bleeding. The type of bleeding experienced does not help distinguish benign or malignant causes, although a gushing type of bleeding is said to be more often associated with malignant than with benign diseases of the uterus. Spotting and scanty flow are the more common complaints. Brewer and Miller[186] have emphasized the fact that there may be only a single episode of spotting or intermittent spotting with intervals of three or more months between episodes. Neither can one assume that bleeding in a patient receiving estrogens is necessarily due to the administered estrogen.[187] Zeit[188] has discussed the problem of uterine fibroids in the menopause and postmenopausal age group, and has pointed out that small myomas must not be blamed for abnormal bleeding until more likely conditions, such as cervical and endometrial polyps, atypical hyperplasia and fundal or cervical carcinoma, have been excluded. Postmenopausal increase in size of a fibroid is indication for removal. Zeit's statistics indicate that asymptomatic myomas, less than the size of a two months' pregnancy, must be carefully watched but usually do not cause trouble.

Discussion of the indications for hysterectomy is not pertinent to this paper, but it should be pointed out that the practice of removing the ovaries of postmenopausal women at the time of hysterectomy, as advocated by some,[189] must be reviewed in the light of increasing evidence that the postmenopausal ovary is a functioning organ. It is generally held that after hysterectomy there is more rapid ovarian failure owing, presumably, to interference with the blood supply to the ovary.[190]

Vitamin E

No clear rationale is apparent for the use of vitamin E in the menopause. Vitamin E does play a part in the reproductive process of some animals, and it has been shown that, in the rat, the "menopause" and sterility occur earlier in animals deficient in vitamin E than in a control group.[191] However, tocopherol deficiency is only one factor in the sterility of the aged rat. No definite difference in tocopherol levels of normal women and women with reproductive disorders has been demonstrated.[192] Numerous clinical reports[192-198] have appeared reporting the beneficial effects of vitamin E in the treatment of menopausal symptoms. McClaren[195] stated that vitamin E helped to heal senile lesions in the lower genital tract. Gozan[199] found vitamin E effective in 50 per cent of menopausal patients but pointed out that the effect may be explained by the pharmacology of placebos. Blatt, Wiesbader and Kupperman[200] recently produced statistical evidence to prove the point that vitamin E is no more effective than a placebo and that any value of vitamin E in the menopause must be ascribed to its placebo effect.

Conclusions

The menopause is a normal phase in which there is a gradual decline of ovarian activity followed by a low but significant level of postmenopausal ovarian function. The menopause is commonly attended by hormonally mediated symptoms, such as hot flashes, but the more publicized symptoms appear to be related to concomitant changes in the life situation. The physician's responsibility to the woman in this phase is clear and consists chiefly in education, reassurance and guidance. Less clearly defined is the management of the postmenopausal state which, in view of rapidly lengthening life span, is becoming an increasingly important problem. There is, as yet, no proof that estrogens will prevent or delay the aging process, and other steroids are probably implicated as well. Rather impressive evidence can be cited, however, for a beneficial action of estrogen on dermal and genital atrophy, osteoporosis and atherosclerosis. The fear that estrogens as used therapeutically are carcinogenic in human beings is not justified by current evidence. The question of long-term steroidal therapy of the postmenopausal woman remains unanswered.

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MEDICAL INTELLIGENCE

TRONOTHANE IN PRIMARY GINGIVOSTOMATITIS*

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PRIMARY herpetic gingivostomatitis can be an extremely debilitating disease. The painful oral lesions, which may last from eight to fourteen days, may interfere with eating and drinking so that parenteral fluid therapy is necessary. Whereas there appear to be some contraindications to the liberal use of the "caine derivatives" for symptomatic relief of this disease, in a recent case study Tronothane§ was found effective and without evidence of toxicity or sensitization.

The Tzanck procedure is an easy and reliable method of confirming this diagnosis.

CASE REPORTS

D.L., a 34-year-old woman, had a past history of recurrent herpes simplex involving the blush area of the right cheek. On the 7th day of a severe recurrence of this disease the patient's 10-year-old daughter acquired a stomatitis associated with fever and cervical lymphadenopathy. The later clinical course and the Tzanck procedure (Fig. 1) proved this to be primary herpetic gingivostomatitis. Within the next week, J.L., 21 months, and K.L., 3 years of age (Fig. 2), manifested the same disease.

In the two younger children the oral lesions were so painful that nutrition and hydration were so much impaired that parenteral fluid therapy was considered.

FIGURE 1. *Smear from the Base of an Oral Lesion of Herpetic Stomatitis, Showing a Multinucleated Giant Epithelial Cell (Giemsa Stain).*

For topical anesthesia 1 per cent aqueous Tronothane was applied liberally by a cotton swab to the involved areas. This treatment produced immediate relief, allowing the children to eat and drink with reasonable comfort. The local anesthesia lasted approximately 2 hours.

Throughout the course of the disease the Tronothane was applied topically to the lesions before meals and at bedtime.

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§Para-buloryphenyl gamma-morpholinopropyl ether hydrochloride — synthesized at and kindly supplied by Abbott Laboratories, Chicago, Illinois.

with the same symptomatic relief. There was no evidence of toxicity or sensitization.

Discussion

Repeated and indiscriminate use of the "caine" derivatives for symptomatic relief of painful oral lesions has been viewed with some reluctance because of the possibility, although rare, of toxic reactions

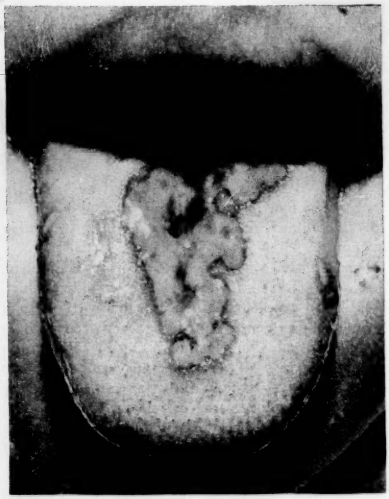

FIGURE 2. *Lesions of Herpetic Stomatitis on the Eighth Day of the Disease.*

manifested by tachycardia, muscular twitching and, in severe cases, convulsion and death. There is also the problem of sensitization, which, when acquired, precludes the further use of these valuable agents. It has been shown that certain "caine" groups produce ineffective anesthesia when applied topically to the mucous membranes.

Tronothane is structurally different from all other topical anesthetics now available. It contains an ether linkage and morpholino radical, both of which differentiate it from other local anesthetic agents and thus reduce the likelihood of cross-sensitization. Toxicity, as evidenced by animal studies and clinical observations, is extremely low. Primary sensitization appears to be negligible.[1]

Although this drug appears to have a wide margin of safety, it should at present be prescribed in limited quantity because of its newness and possible indiscriminate use by well meaning parents for this disease.

It is relatively easy to differentiate herpangina from primary herpetic gingival stomatitis on a clinical basis. In the former the lesions are confined to the tonsillar pillars and soft palate, and the disease occurs only during the summer months. Herpetic stomatitis may occur at any time and produces a more generalized distribution involving the gums, lips, tongue and buccal mucosa. In addition, there is gingival hyperemia and hypertrophy, which cause the gums to bleed easily.[2] However, since the oral lesions of herpangina persist for only four to six days and its course is milder than that of herpetic stomatitis, in which the lesions last for eight to fourteen days, with a stormier course, it is important to establish a definite diagnosis. This can be done by means of the Tzanck procedure.[3] Material is scraped from the floor of a lesion, placed on a slide and stained with the Giemsa technic. The presence of epithelial giant cells is found in only three viral diseases: herpes simplex, herpes zoster and varicella. The clinical manifestations of the herpes-simplex virus, such as the ordinary cold sore and herpetic stomatitis, are easily differentiated from the other two viral diseases.

This report certainly agrees with the statement of Scott et al.[4] that in a susceptible population the disease is highly contagious. In addition it appears that the stomatitis was acquired from an adult with cutaneous herpes simplex.

Summary and Conclusions

In these cases Tronothane was an effective and safe anesthetic for the relief of discomfort associated with herpetic stomatitis. The disease is highly contagious and may be acquired from cutaneous herpes simplex. The Tzanck procedure is a simple confirmatory diagnostic method.

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DOCTORS AFIELD

Usher Parsons

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DR. Usher Parsons was not one of the outstanding surgeons of the country but he had an excellent training, unusually good associations and an interesting career, being best known as the surgeon hero of the Battle of Lake Erie, under Commodore Oliver Hazard Perry.

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He was born at Alfred, in the point of Maine running down southwest to the Piscataqua River, Kittery and Portsmouth. His early education was fairly good. He went to the village school when he was not working on his father's farm, and then a year at Berwick Academy brought him to the age of thirteen. Work in retail stores at Portland and Kennebunk until he was nineteen was presumably the equivalent of Harvard Business School. Having thus assured his economic future, he entered the office of a local doctor as a medical student. Of course, he taught school from time to time, as did all the young men who wanted to use their brains. Usher Parsons said, when at nineteen he decided to study medicine, "I had no means of educating myself but by school keeping." That was not strictly true. When he wished another course of lectures on anatomy he proceeded as follows:

> I walked fifteen miles in the night, nearly to Saco, slept a few hours on some hay in a barn and reached Kennebunk the following noon, and Alfred in the evening . . . On arriving at Alfred I packed up my Latin books and placed myself in the family of Parson Sweat. I began with the Latin grammar and by the last of November had gone over it several times and read two books in Virgil and was able to read the Greek testament a little. I then taught school two months in Elliot; then returned to Parson Sweat a few months; then went in May to keep school three months half a mile from Berwick Academy; then attended the academy one quarter and read Greek and four orations against Cataline; then kept school at Alfred three months and read Virgil and Greek in the evenings . . . I then went to Boston and entered the office of Dr. John Warren for six months. It was with some difficulty that I got through with the expense of lectures and board although assisted to fifty dollars by my father.

What a glimpse into another world! No transportation in a school bus. That fifty dollars could not have bought his cigarettes today. And Latin and Greek — this might just as well have been centuries ago.

But he had one remarkable piece of medical education. John Warren was the first of four generations of John Warrens, professors at Harvard Medical School, and one of the founders of this school. John's brother, Joseph Warren, was killed at Bunker Hill. John, to prove the genuineness of his attitudes, bequeathed his own skeleton to the Warren Anatomical Museum at Harvard. To be apprenticed to such a man as that was as high as Usher Parsons could have gone in preparing for medicine. By the time he had finished this apprenticeship and was licensed as a practitioner in medicine in Massachusetts it was 1812, a famous date in American annals, for then began the War of 1812.

Of course, Usher Parsons made moves to get into the war activities, and after the usual necessary delays and bunglings involved in governmental activities, he was commissioned surgeon's mate in the Navy and in October was taking his first voyage: across New York state in wagons.

During the following summer "bilious remittent fever," presumably malaria, set in. Usher himself was sick, but not as much so as the other surgeons. Hence, when Captain Oliver Hazard Perry sailed to meet the enemy, he had only one surgeon in the fleet of about half a dozen vessels. This was Usher Parsons.

Naval battles in those days were not gentle affairs. The vessels were of wood, without armor, and the procedure was to get as close to each other as possible and let fly with cannon balls, chain shot and canister. Hence, not only these missiles but the huge splinters of wood and the falling spars helped to create havoc.

As for the Battle of Lake Erie, the forces involved were small to be sure, but importance, despite the modern attitude, is not directly determined by size. At the beginning of the war it was the plan of the Americans to invade and annex Canada. This had not worked out well, and there was the possibility of a turnabout. After Perry had cleared the Lakes of the British fleet this left the States free from the danger of a flanking attack from this direction. It was difficult to whip the Americans from any other direction.

However, this was not Usher Parsons's problem. He was there to care for the sick and wounded, which he did in an excellent manner. In this battle he had the unique experience of being the only surgeon in an important naval engagement. Out of 150 men on the Lawrence over 80 were killed and wounded. Since the Lawrence was shallow draft the wardroom where he worked was above water and 10 by 12 feet square — the size of a modern prize-fight ring. One thing was to his advantage: he was too busy to worry about cannon balls or to duck them. Plenty went through. He was not the only unperturbed one on board, as suggested by the following extract from his diary:

> When the battle had raged an hour and a half I heard a call for me at the small sky light and stepping towards it I saw it was the commodore, whose countenance was calm and placid as if on ordinary duty. "Doctor," said he, "send me one of your men," meaning one of the six that were to assist me, which was done immediately. In five minutes the call was repeated and obeyed and at the seventh call I told him he had them all. He asked if they could pull a rope, when two or three of the wounded crawled upon deck to lend a feeble hand in pulling at the last guns.

The wounded stayed right where they were for several days, and a few days later, the wounded of the whole fleet were brought there, about 100 in all. Perhaps the fact that they could not be moved at first was a blessing to them. Parsons attributed his general success with the wounded to the fresh air (they were lodged on the deck of the Lawrence, sheltered by an awning and tarpaulins), a plentiful supply of fresh vegetables, provisions and cordials and the cheering influence of victory. Thus, with rest, fresh air, good food, a little courage from the cordials and a psychosomatic effect, the physicians of that day did well enough without antibiotics, cortisone or vitamins.

Parsons received a silver medal with a likeness of

Perry and a share of prize money that gave him a feeling of pecuniary independence. He used the cash to pay the debts of his medical education. He was soon promoted to the rank of surgeon. Then Perry was given command of the new frigate *Java,* was allowed to choose his officers and selected Parsons as one.

He and Perry went to the Mediterranean on the *Java.* Usher Parsons's diary, which he kept carefully for many years, is a most interesting description of his travels, for he knew what to take an interest in and how to tell of it: Etna, Pompeii and about everything in between, with much in Northern Africa and Gibraltar. With all this he was back at the age of twenty-nine, and this experienced surgeon finally, with more study, got his medical degree from Harvard a year later.

Shortly thereafter he went to Europe again on the frigate *Guerrière,* which had, to the great surprise of the British, been defeated by the *Constitution.* His story of this cruise, the places he visited and the worth-while people he became acquainted with makes interesting reading in his diary. One important result of all this was the advice and the introductions that he could give to his young brother-in-law, Oliver Wendell Holmes, when the latter pursued his medical studies abroad. Dr. Holmes's later story was a delight and inspiration to young men with medical ambitions who came after him. Few realize how much he owed to Usher Parsons.

Fortunately, at the end of this cruise, Parsons was ordered to serve at the marine barracks at Charlestown, Massachusetts, for he lived much of the time in Cambridge, and became acquainted with the family of the Reverend Abiel Holmes, D.D. Of the brilliant children in this family, Dr. Holmes, twenty-one years younger than Dr. Parsons, is the best known, but John and Mary were thought by many friends to have fully as good minds. Two years later Mary became Mrs. Usher Parsons and settled in Providence.

Parsons got into the medical game promptly, for the Brown Medical School was then established, and in the year of his marriage he became professor of anatomy and surgery. He had always had an ambition to be a professor, and two years before this he had had such a professorship for a short while at Dartmouth.

The story of the Brown Medical School is tragic. It had a short but brilliant career, with a small, able faculty, and several of its graduates were distinguished. President Wayland, who had been himself trained in medicine, evidently believed, with the earlier Cotton Mather, that medicine and religion should be inseparable. It is difficult to give much credit to the reason he produced for killing the school. He announced that, for purposes of discipline, all faculty members must dwell on the campus. Since the medical-school professors had families and private practices on which they relied for support, it followed, as President Wayland knew that it must, that the medical school was ended.

One may realize now how this injured medical education and the care of the sick. I am told that there is not anywhere in the country an area with so large a concentration of population as around Providence that is unprovided with a medical school. There are the necessary hospitals and trained personnel, which all medical educators agree do their best work in connection with a school. But where is the $25,000,000 needed to develop one now?

Early in his career, in fact when he was living in Cambridge before he opened practice in Providence, he wrote the *Sailor's Physician,* a medical guide for use on merchant vessels. Later the name was changed to "Physician for Ships." It sold extensively and went through five editions in fifty years. This had probably as good directions as could be given to masters of vessels for the treatment of the diseases of their crews; since practically nothing was known in those days of the causes of infectious diseases, Parsons's work naturally did not amount to much. The best that could be said for it was that it did not encourage overtreatment, as many treatises did. The general rules of hygiene were remarkably good. Thus, he described the precautions to be taken against that most pernicious accompaniment of long voyages, scurvy. He stressed what I have not heard recommended much: potatoes. I assume that these are as easy to keep in good condition as any vegetable or fruit available.

Although he knew nothing, of course, of the role of mosquitoes in malaria, he told ship captains to moor their vessels, if possible, where the effluvia of marshes would not blow down on them; since the mosquitoes came down wind with the effluvia, that was good advice. Anyway, a book that went through five editions in half a century must have impressed its readers.

I do not know how many today would approve of his religious ways. When he was about fifty years old, he wrote as follows:

> I have this day finished the Old Testament. I cannot but think that the Christian religion would gain by excluding some of the books.

Also, his churchgoing was unusual. He was born a Congregationalist, but soon after marrying the daughter of a Congregational minister and sister of a Unitarian, he joined the Episcopal communion at St. John's Church. He had seats at First Baptist, St. Stephen's and Central Congregational. He was especially fond of the Unitarian under the ministry of Dr. Edward B. Hall. Still, after hearing him on Thanksgiving, he wrote:

> I wish he and other Unitarians would preach a little more about Christ and he crucified. At the same time I wish the Orthodox would not be forever harping on particular doctrines of the Calvinistic order.

He filled in his spare time with genealogies of numerous families. He was an authority on the

Indians of Rhode Island. He wrote a life of Sir William Pepperrell, who, I think, was the only New England baronet; at any rate he was the brilliant leader of the colonists at the first capture of Louisburg. Right here I have tied Dr. Parsons: I also have viewed the ruins of that famous fortification.

The last public appearance of Dr. Usher Parsons was at the opening of the Rhode Island Hospital. He died in 1868, and in keeping with his religious versatility, his funeral was conducted by the pastor of the Beneficent Church.

The well known portrait of him shows an elderly man with rugged features, typical of the New England states. He might well have been a chief justice of Massachusetts, a prosperous Maine ship owner or an early governor of Rhode Island. He escaped being merely a doctor of medicine by being a naval officer in the days of wooden ships and iron men. He probably was a prosy, prejudiced patriarch, but I suppose that lots of able men develop into that. In his middle age he was evidently respected and even loved by his brilliant brother-in-law, Dr. Oliver Wendell Holmes, who sent home from his medical studies in France two skeletons, the smaller one for himself and the larger for his brother-in-law, "as I supposed the doctor would like the more showy one." In the John Hay Library at Brown University is a letter from Holmes to Usher Parsons, written when the latter was fifty-six and the former was thirty-five, which reads as follows:

> I sent a trusty emissary to the Providence R.R. depot yesterday and day before yesterday morning — but there was nothing there for me.
>
> Has anything happened to prevent our still friend from coming? Please drop a line, explaining mishaps and recounting adventures.
>
> Yours in immediate haste,
>
> OWH

Evidently, Holmes visited Providence often. Thus it was that he found the finest of all elms at Johnston. Parsons must have been an unusual man to interest and hold Holmes as he did.

Samuel Prescott and His Midnight Ride

HENRY R. VIETS, M.D.*

BOSTON

DR. Samuel Prescott, son and grandson of Concord physicians, had ridden, during the evening of April 18, 1775, to call on Lydia Mulliken, daughter of a Lexington clockmaker. On the way home, early in the morning of April 19, he learned that Paul Revere and William Dawes had brought the news that the British were on the march from Boston.

Spurring his horse, he overtook the midnight couriers on a road that ran through the northern part of Lincoln. While Dawes was stopping to arouse a family of sleeping farmers Revere rode ahead and at a bend of the road was held up by four British officers. When Dawes saw that Revere had been captured he turned back and escaped the way that

FIGURE 1.

he had come. Prescott went to Revere's aid, but the opposition was too much for him since he had only the butt end of his whip as a weapon against four men armed with pistols and swords. "Put on!" he cried to Revere and jumped his horse over a stone wall and made off into a ravine near a swamp. Revere also escaped, only to be recaptured a short time later.

FIGURE 2.

Prescott had the advantage of maneuver, for he knew the country well, and speeding on to Concord, finished the alarm that Revere and Dawes had started, enabling the Minute Men to assemble and conceal most of the stores in Concord before the British arrived.

Thus, Prescott, not Revere, got the news to Concord, but the exciting events that followed almost erase from history the picture of Lydia Mulliken and her gallant lover. Prescott "joined up," served at

*Curator, Boston Medical Library.

Ticonderoga in 1776 and was taken prisoner and carried to Halifax, where he died in jail the next year, almost forgotten except for his epochal ride.

FIGURE 3.

Revere, in a letter to the Reverend Jeremy Belknap, written on January 1, 1798, pays tribute to Prescott, "a high Son of Liberty," and it is from Revere's own account that much of the narrative outlined above is derived.

Figures 1-3, reproduced through the courtesy of the Collyer Collection, Bennington Historical Museum and Art Gallery in Bennington, Vermont, have been attributed to Thomas Sully (1783-1872), who later became famous as a portraitist. Presumably, this fanciful depiction of Prescott's courting and its immediate aftermath was one of his early works, similar to the better known historical painting, "The Capture of Major André." The pictures of Prescott seem primitive, and the story depicted is historically inaccurate. There is no evidence that the news of Revere's alarm was received by Prescott until after he had left Lydia or that she urged him to ride and even provided him with a crude weapon for his defense. Although the pictorial narrative, indicating a reluctant youth urged to action by his feminine companion, is not accurate the three pictures have some sentimental value, for few physicians have been so rescued from oblivion even by an artist's misconception of a moment of sentimental love-making before a night of great significance in American history.

CASE RECORDS
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Weekly Clinicopathological Exercises

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CASE 42161

PRESENTATION OF CASE

A forty-three-year-old man entered the hospital because of hemoptysis.

About fifteen years previously there was an episode of "pleurisy" associated with moderate cough and hemoptysis and relieved by bed rest. Since then the patient had had a mild morning cough productive of a minimal amount of nonmalodorous phlegm. Twelve years before admission there was an episode of mild hemoptysis. Two years later an episode of gross hemoptysis was noted. X-ray films of the chest were allegedly normal, and a gastric aspiration yielded bloody fluid. In the past he had occasionally coughed up yellow calculi. This had occurred more frequently between nine and six years before entry and was not associated with hemoptysis. Two years before admission there was an episode of "pneumonia," with fever and malaise but without cough or pain in the chest. An x-ray film of the chest showed a "scar" in the right lung. Seven months before admission he had a mild upper respiratory infection, with a slight cough, fever and tightness in the chest. An x-ray film of the chest again showed a "scar" in the right lung. The infection subsided with oxytetracycline (Terramycin) therapy. Two weeks before entry he had another upper respiratory infection, with fever, mild cough and a temperature of 100°F. He recovered in two days with Terramycin therapy. Two days before admission there were about five episodes of hemoptysis, with production of a total of 60 ml. of bright-red blood. On the next day there was another similar episode of hemoptysis. A film of the chest showed the same changes as those noted on the film taken seven months previously.

The patient smoked 1 or 2 packages of cigarettes daily. Except for brief visits to California, Florida and Cuba he had lived all his life in Virginia and New Hampshire. There was a past history of excessive alcoholic intake.

Physical examination revealed a well nourished man who had a mild cough productive of whitish sputum. Examination of the chest showed diminished breath sounds and occasional fine rales over the right-lung base posteriorly. The heart was normal.

The temperature was 98.6°F., the pulse 70, and the

respirations 20. The blood pressure was 130 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 14.2 gm. per 100 ml. and a white-cell count of 8400. The urine was normal. Smears of three sputum specimens were negative for acid-fast bacilli. Cytologic examinations of the sputum for malignant cells were negative and unsatisfactory. A P.P.D. tuberculin skin test (first strength) was positive in twenty-four hours. X-ray films of the chest demonstrated several scattered calcified lesions in the basal segments of the right lower lobe (Fig. 1) and what appeared to be calcified lymph nodes at the lung roots; there was some crowding of the markings in the anterior basal segment of the right lower lobe; a few of the calcium deposits appeared to be in close relation to the right intermediate bronchus; the left lung was normal. A bronchogram showed filling of all the bronchi; there was some clubbing and irregularity of the ends of some of the right-lower-lobe bronchi; at several of these points the defects were superimposed upon the pulmonary calcifications. A bronchoscopic examination was negative except for fresh blood in the right-lower-lobe bronchus.

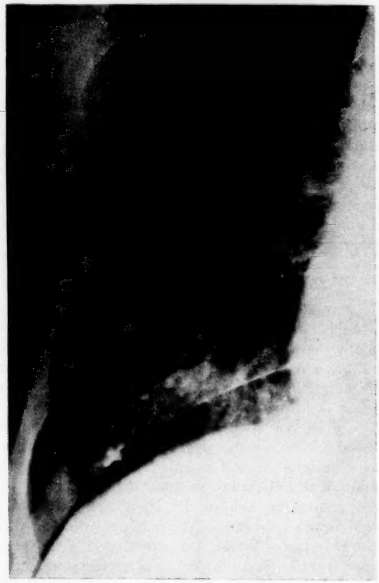

FIGURE 1.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LAMAR SOUTTER*: May I look at the x-ray films?

DR. C. C. WANG: The films of the chest show flecky calcifications in the right-lower-lung field, mainly in the subsuperior segment of the right lower lobe (Fig. 1). The remaining lung fields are clear. There may be some calcification adjacent to the right pulmonary artery. The heart is not enlarged. The diaphragmatic shadow and the bones are not unusual. Bronchograms demonstrate minimal dilatation of the bronchi in both lower lobes but no definite evidence of bronchiectasis. I cannot be sure whether the previously noted calcifications in the right lower lobe may lie inside or outside the bronchi.

DR. SOUTTER: Essentially, this is a problem in the differential diagnosis of hemoptysis. In a fifteen-year period this man had four severe bouts of hemoptysis and four febrile episodes associated with pulmonary symptoms. In addition he had a chronic cough, productive of whitish sputum. We know certain things about him. In the first place he had bronchiectasis as demonstrated by x-ray study. Secondly, he had probably had tuberculosis at some time because a first-strength tuberculin test was positive; whether or not the tuberculosis was active at the time of admission is another matter. The sputum was negative by smear for tubercle bacilli, but until three negative cultures of sputum and three negative gastric washings are obtained one cannot completely eliminate the possibility of active tuberculosis. The roentgenograms of the lungs did not give evidence of activity, however, which is additional evidence that the disease was quiescent. Whether or not he had had it in the past, possibly with the first episode of pleurisy, fifteen years before entry, I cannot tell.

We also know that he coughed up calculi. These come from the erosion through a bronchial wall of particles of a calcified lymph node in the hilus of the lung. The patients who have this trouble usually bleed either before or after they cough up the calculus. On bronchoscopy, a small ulceration in a main bronchus at the site where the calculus has penetrated may be seen. Sometimes another calculus that has not completely eroded through the bronchus may also be seen protruding through the membrane. Under certain circumstances — when there are repeated episodes of bleeding — it may be necessary to remove the calcified lymph nodes surgically. Most of the persons who have broncholiths have a considerable degree of calcification of the lymph nodes of the hilus. This man's areas of calcification were confined to the periphery of the lungs.

Patients with even a small amount of bronchiectasis are known to bleed; the blood is usually bright red, and the bleeding may be massive or may be only

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small in amount. However, in the differential diagnosis of hemoptysis, there are a great many conditions to consider. I think that I can assume that this man did not vomit the blood in spite of the fact that on one occasion blood was found in the stomach. He may have swallowed blood after coughing it up. He could have bled as a result of trauma from the Levin tube or of disease in the esophagus or stomach that was not apparent.

Among the main conditions that we must consider in this case are acute and chronic inflammatory diseases. Tuberculosis I have already mentioned. I believe that there was some residual tuberculosis. Sarcoidosis is another possibility. It is a granulomatous disease that is usually characterized by enlarged hilar lymph nodes with or without miliary changes in the lung itself. There was no record of such changes in this patient. Although sarcoidosis can be atypical in its manifestations, it seems to me that I am correct in assuming that this patient did not have it.

Some of the fungi, such as actinomyces and blastomyces, when they invade the lungs, may cause pathologic changes resulting in hemoptysis on occasions. Patients with these infections usually have enlarged lymph nodes. Moreover, the process radiates out from the hilus of the lung. Also, in the active phase of the disease, when there is hemorrhage, the organism may be identified in the sputum, and the x-ray picture is usually characteristic. Other types of diseases in which there may be calcification are histoplasmosis and coccidioidomycosis. Histoplasmosis occurs in about 25 different states, especially in those in the Mississippi Valley. Since people travel about this country so much, it is possible to find someone who has it in any state. Histoplasmosis in the lungs is usually a diffuse process; when it becomes chronic and regresses, the lesions often become calcified. In the regions in which histoplasmosis is endemic, positive reactions to the skin test for this disease are frequent. It is possible for persons living in those areas to have both histoplasmosis and tuberculosis. The calcifications of histoplasmosis resemble the small areas of miliary tuberculosis that have calcified; there is a fairly diffuse peppering of these in both lungs.

The lesions caused by coccidioidomycosis will also calcify as they become chronic. In patients who have had only mild symptoms, such as this patient had, and in whom the disease is under control, there may be small areas of calcification. The calcification, however, is usually single and looks more like that seen in a tuberculoma, though there may occasionally be multiple areas of calcification. In the areas in which this disease is endemic, such as the San Joaquin Valley in California, or parts of Arizona, among patients with pulmonary calcifications seen roentgenographically who do not have a positive tuberculin test the skin test for coccidioidomycosis will be positive in a high percentage of cases. The percentage of positive tests on all persons living in the endemic areas is very high and some have both a positive tuberculin test and a positive test for coccidioidomycosis. I should eliminate that disease in this patient because the areas of calcification were multiple. I shall also eliminate the possibility of histoplasmosis although I cannot positively rule out either disease simply because in this part of the country they are unusual.

Could this patient have had tumor associated with bleeding? If he had tumor, what kind was it? Was it a carcinoma? Although he was young, he was a persistent, heavy smoker and had raised sputum daily for a number of years. Carcinoma would not, however, explain the episodes of bright-red blood for fifteen years, nor can I correlate carcinoma with the previous bouts of fever. Carcinoma may have calcium in association with it. Most of us believe that in such cases the carcinoma has arisen next to an old, healed tuberculous lesion or another calcified process and that actually the calcium is not part of the tumor process. It is also inconceivable that if an adenoma had been present, it would not have been seen roentgenographically or bronchoscopically.

In conclusion I think that the patient had had tuberculosis and that it was probably not active on admission. He had minimal bronchiectasis in the right lower lobe and associated areas of calcification. I do not know whether the calcification was the result of tuberculosis or was laid down in the bronchial wall as sometimes occurs in a healing infection associated with bronchiectasis.

How am I going to explain the hemoptysis? The simplest explanation is that a broncholith had eroded through a bronchus or that a piece of calcium had torn away from the inside of a previously infected bronchus and was coughed up and that that was the source of the hemorrhage.

DR. BENJAMIN CASTLEMAN: Dr. Scannell, you saw this patient.

DR. J. GORDON SCANNELL: I should like to think that our differential diagnosis was as complete as Dr. Soutter's. We reached about the same conclusions as he did, although we were not so impressed by the possibility of tuberculosis, but were impressed by the scattered calcifications in the right lower lobe. After the hemoptysis lessened we asked the patient whether he had ever coughed up anything that looked like stones. He said that it was strange that we should ask him that, for about five or six years previously on three or four occasions he had coughed up something about as large as the head of a match that was yellow and gritty. He cut it in half, and it tasted and smelled unpleasant. He had not coughed up stones for three or four years. We were enthusiastic about that discovery and thought he had a broncholith in the region of the bronchiectasis. I think we also believed that this was the logical explanation for the bleeding. Bronchoscopy shortly after admission showed that the bleeding, though it had stopped, appeared to have come from the right lower lobe only. Since it had

stopped, to be sure of the diagnosis, we did an exploratory thoracotomy a week later and removed the right lower lobe.

Clinical Diagnoses

Bronchiectasis.
Broncholithiasis.

Dr. Lamar Soutter's Diagnoses

Healed tuberculosis, with formation of broncholiths.
Bronchiectasis.

Anatomical Diagnosis

Broncholithiasis.

Pathological Discussion

Dr. Castleman: The specimen that we received showed a piece of calcium in one of the bronchial branches just below the point of resection. There

Figure 2.

were two stones in one of the main bronchi to the right lower lobe. The wall of that bronchus was very thick compared to the others. The entire wall was gritty and contained large numbers of spicules of calcium. On palpating the rest of the lobe we could feel about a dozen calcified nodules — most of them beneath the pleura, out in the periphery of the lung (Fig. 2). The nodules were almost encapsulated and sealed off from neighboring bronchioles. When we examined this microscopically we found the area of calcification embedded in fibrous tissue. In some areas the calcification had ossified (Fig. 3). The section through the thick-walled bronchus revealed cartilaginous plates with many areas of calcification and of true bone formation. In many of the sections we found some actual bone marrow. This suggested very strongly that the cartilage degenerated, calcified and then ossified, which is a finding that we see in elderly persons, but rarely in young persons. I think most physicians believe that the cause of lithiasis of a

Figure 3. *Photomicrograph, Showing Three Foci of Calcification, the Lower One with Ossification.*

bronchus is, as Dr. Soutter suggested, the erosion of a calcified, usually tuberculous lymph node through a bronchus. We looked carefully in this specimen, but did not find any calcified lymph nodes. On the other hand, I gather that there are calcified lymph nodes in the hilus; Dr. Wang says that they are still there after removal of the right lower lobe.

Dr. Scannell: They are still present in the region of the upper lobe.

Dr. Castleman: I believe that the stone originated in the wall of the major bronchus. Whether it occurred a few years after the pneumonia — that is, whether at that time there was enough bronchitis or degeneration of the cartilage with calcification to produce the stone, I do not know. At any rate tiny pieces broke off and perhaps showered emboli to the rest of the lobe, in the same way in which pieces of a large thrombus in the pulmonary artery, or a major vessel, break off and shower the rest of the vessels in

the lung. That is one possibility. The other possibility is tuberculosis in the lobe, but we found no evidence of any tuberculous focus; perhaps it had completely healed.

DR. SOUTTER: There may have been tuberculosis in another lobe.

DR. CASTLEMAN: Yes.

DR. SCANNELL: It is of interest that in the upper lobe there was very little scarring, and on palpation it appeared to be quite normal. This lower lobe was very shrunken except for the apical segment. The calcification was peripheral, and there was a great deal of scarring and puckering of the lobe. I think, as Dr. Soutter suggested earlier, that this may well have represented a reaction to chronic infection in the wall of a bronchiectatic cavity, and that it was completely diffused.

DR. CASTLEMAN: There was not much bronchiectasis. We dissected out all the bronchi, which looked perfectly normal. On the films there really is not much bronchiectasis. The major disease was in the one bronchus that contained large stones. All the flecks of calcification in the periphery seemed to be encapsulated at the ends of bronchioles — not in the parenchyma.

DR. EARLE M. CHAPMAN: Were any studies on the blood calcium made?

DR. SCANNELL: No.

DR. CHAPMAN: This may have been an independent entity of a nontuberculous nature and perhaps noninfectious; it may have been a metabolic disorder.

DR. CASTLEMAN: It would be surprising to see it localized to one lobe; usually when there are changes in the lungs in metabolic diseases that produce areas of calcification — for example in hyperparathyroidism — the calcification is in the lung parenchyma, in the alveolar walls, not in the bronchi.

DR. HELEN S. PITTMAN: About tuberculosis, I think that the positive skin test may have been a "red herring" because it was positive at the end of twenty-four hours; the tuberculin test is readable at forty-eight hours. It is possible that that was a transient reaction to some other condition and not a true positive tuberculin test.

DR. CASTLEMAN: In a very good paper reported from the Mayo Clinic on broncholithiasis Schmidt and his associates[1] referred to the fact that calcification was seen by Aristotle in 300 B.C. They also mentioned a paper published in 1600 and one in 1689 by Morton,[2] which really is amusing. Morton wrote in Latin and outlined the treatment of this disease:

> First; in the beginning of the disease lubricating medicines should be used copiously; yes, and mild emetics, by which one attempts to promote the expulsion of the calculus or of other bodies that have lodged in the lungs since long delay makes it more difficult to expel them and the condition of the lungs is thence more gravely injured. Secondly; if, however, severe and spasmodic pains are excited by the laceration of the lungs caused by motion of prickly calculi of this kind, copious hemoptysis is to be expected; and therefore instead of lubricating medicines, laudanum should be given freely and frequently, by which the motion of the calculus can be stopped promptly, pain can be relieved and hemoptysis can be checked. . . . Certainly if phthisical patients of this kind take care of their health, as by always breathing pure country air, avoid taking cold, drinking bouts, excessive exercise and whatever else can excite the fixed calculi to new movement, they will be able to live to an advanced age, performing their usual duties satisfactorily. . . . Only when there is urgent need should a milk diet be ordered in phthisis arising from pulmonary calculi, because such a diet is likely to generate new chalky stones of this kind in the lungs.

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CASE 42162

PRESENTATION OF CASE

A seventy-two-year-old man entered the hospital because of anorexia.

About seventeen years previously he noted the gradual onset of dysphagia, dysarthria, muscular weakness, ptosis and diplopia for five months. With neostigmine (Prostigmin) and ephedrine therapy he became asymptomatic and returned to work. The blood pressure was 180 systolic, 90 diastolic. The blood Hinton test was negative. Six years later he was still asymptomatic and was taking 1 to 3 neostigmine tablets daily. During the five years before admission he became dyspneic when climbing one flight of stairs. Four weeks before entry there was an episode of palpitation associated with dyspnea. For three or four weeks before admission there was anorexia, with increasing fatigue, weakness and lassitude. There had been no diplopia.

For ten to fifteen years the patient had noted constipation, which had become worse during the six months before entry. During the ten years before admission he had had "bronchitis," with an intermittent cough productive of 1 or 2 tablespoonfuls of thick, yellowish sputum daily. The cough had been slightly worse during the month before admission. The temperature had been normal. Six years before entry he was admitted to another hospital because of weakness, fatigue, anorexia and pallor. Examination of the blood revealed a red-cell count of 640,000, with a hemoglobin of 2 gm. per 100 ml., and a white-cell count of 3650. On smear there was marked macrocytosis. He improved with blood transfusions and vitamin B_{12} therapy. For five years before entry there had been occasional dizzy spells, with left-sided tinnitus and lightheadedness, that were relieved when he lay down for five minutes. Drugs that he had taken until the time of admission included neostigmine, 15 mg., six times daily, ephedrine sulfate, 25 mg., six times daily, vitamin B_{12}, liver extract, ferrous sulfate and erythromycin.

Physical examination revealed a fatigued, cachectic man. The tongue was red and smooth. There was no ptosis or diplopia. Examination of the chest showed an increase in the anteroposterior diameter, with dorsal kyphosis. There was poor diaphragmatic movement. Fine moist rales were audible anteriorly, most prominently in the parasternal areas, and at both lung bases posteriorly. The upper border of liver dullness was at the sixth right intercostal space; the liver edge was felt 1 or 2 cm. below the costal margin. The spleen was not palpable. Neurologic examination was negative. Rectal examination revealed a fecal impaction.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 130 systolic, 70 to 40 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14 gm. per 100 ml. and white-cell counts of 15,050 and 20,500, with 73 per cent neutrophils. The nonprotein nitrogen was 41 mg., and the cholesterol 309 mg. per 100 ml. The prothrombin content was 74 per cent. Cephalin flocculation was ++ in forty-eight hours. Thymol turbidity was 10.5 units, and flocculation +++. The blood Hinton test was positive. The uptake of radioactive iodine was 15.6 per cent in twenty-four hours. Sputum smears were negative for acid-fast bacilli, and culture grew out abundant *Haemophilus influenzae*. An ergogram was questionably consistent with mild myasthenia gravis. X-ray films of the chest demonstrated advanced pulmonary fibrosis with emphysema and a superimposed punctate infiltrate throughout both lower-lung fields; there were advanced degenerative changes in the dorsal spine; the heart and mediastinal structures appeared normal. An upper gastrointestinal series showed some irregularity and widening of the mucosal folds in the distal esophagus; the esophagus remained distended with air during most of the examination, but fluoroscopically peristaltic activity appeared to be normal; the stomach was normal. A stool guaiac test was negative.

Lumbar puncture yielded clear cerebrospinal fluid at an initial pressure equivalent to 105 mm. and a final pressure equivalent to 75 mm. of water; the protein was 20 mg. and the glucose 98 mg. per 100 ml.; the Hinton test and gold-sol curve were negative. With penicillin and streptomycin therapy the temperature ranged between normal and 99.2°F. During the first hospital day the patient was given 450 mg. of neostigmine and 150 mg. of ephedrine. On each of the next two days he received 75 mg. of neostigmine and 125 mg. of ephedrine. On the fourth hospital day therapy included 60 mg. of neostigmine and 100 mg. of ephedrine. These drugs were then omitted. There was an increase in appetite after thyroid was given. On the morning of the fifth hospital day, after an enema, the patient had many loose bowel movements and complained of weakness. Subsequently, he seemed cold and sweaty, with nasal secretions and drooling from the mouth. There was no diplopia, and he was able to swallow a glass of water without dysphagia; 15 mg. of neostigmine was given. About two hours later he became progressively more cold and sweaty, pale, obtunded and cyanotic. The pulse was 40 and regular, the respirations 10, and the blood pressure unobtainable. An electrocardiogram showed a bradycardia from a ventricular focus at a rate of 10 to 20. He died in spite of intravenous administration of epinephrine, intramuscular injection of neostigmine and artificial respiration.

Differential Diagnosis

Dr. William Timberlake*: This man's symptoms began at the age of sixty-five years, which is six years before the usual age at onset of myasthenia gravis for male patients in the clinic here. In contrast the age at onset for women is twenty-one years.

One of the early symptoms was muscular weakness. This term may have been chosen to summarize the spotty weakness of muscles of the trunk and extremities, which is usually asymmetrical in myasthenia. It may refer to a generalized feeling of weakness and lassitude, which some patients experience in addition to the easy tiring of specific muscles.

He also had increasing weakness of muscles supplied by the cranial nerves. These muscles are usually, but not always, affected, and their involvement, too, is generally asymmetrical. There are other causes of progressive cranial-nerve paralysis such as tumor, aneurysm, progressive muscular atrophy and basal meningitis. In myasthenia gravis rapid tiring of the affected muscles can often be elicited in the history or demonstrated by repeated use of the muscles. Improvement in muscle strength after rest may also be clear. When there is doubt the other possibilities should not be overlooked, and if a neostigmine test is decided upon it should be given with care. The test ampoule contains atropine to lessen neostigmine's muscarinic stimulation of smooth muscle and glands, but it does not prevent its nicotinic stimulation of skeletal muscle. In nonmyasthenic patients the resultant fasciculations weaken the muscles. Such weakness added to partial weakness from other causes may be fatal. When there is any doubt the first test dose should be 0.5 ml. or less. The risk can also be lessened by use of the shorter-acting Tensilon.

In the case under discussion the diagnosis of myasthenia gravis was established as apparently mild by complete control with 1 to 3 neostigmine tablets a day. We are not told whether the patient had occasional muscarinic side effects. Probably, ephedrine was given for control of these rather than for its added antimyasthenic effect.

Three other systems were affected by chronic diseases. I should like to discuss them briefly before returning to the myasthenia gravis and the terminal episode.

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Fifteen years or so before admission the patient had slight hypertension. We read no more of this. However, ten years later he had palpitations, dizzy spells, lightheadedness and left-sided tinnitus relieved by his lying down. These suggest arteriosclerosis. Ephedrine has to be used with caution when there is hypertensive or arteriosclerotic cardiovascular disease.

The pernicious anemia, diagnosed six years before the final illness, was adequately treated, as indicated by the normal hemoglobin and the absence of neuropathy on neurologic examination. The tongue remained smooth and red but was not sore. A complicating gastric carcinoma as the cause of the anorexia, fatigue and so forth was excluded by the gastrointestinal series. I do not believe the pernicious anemia played any part in the terminal events.

The pulmonary fibrosis and bronchiectasis present for ten years were adequate explanation for the increased thymol turbidity and flocculation. The use of iodine expectorants may be the reason for the impaired uptake of radioactive iodine. I think that the pulmonary disease accounted for the symptoms leading to the final hospitalization and was important in the final chain of events.

In some as yet unknown manner myasthenia gravis is apt to be aggravated by even minor infections. For this reason infections should be controlled as promptly as possible, and the patient should be carefully observed for increasing weakness of specific muscles, necessitating an increase in neostigmine. We are not told when or why this patient's neostigmine was doubled some time before entry. The dosage may have been increased because of the increasing generalized weakness during the last month. It may have been done earlier, which raises the serious consideration that the weakness may have been due to overdosage with neostigmine. Fasciculation may be overlooked by the patient and physician, and the ephedrine may be sufficient to mask the other side effects. When weakness is generalized, one must proceed with special caution or end up unwittingly treating the weakness of neostigmine toxicity with more neostigmine. When antimyasthenic drugs with slight muscarinic effect are used or when the muscarinic side effects of other antimyasthenic drugs on the bowel are masked by atropinelike drugs, irreversible toxic levels may be reached before one is aware of it. Death has resulted.

On admission there was no diplopia. The muscles previously involved are apt to be affected in an exacerbation of myasthenia. No weakness was disclosed by the muscle testing in the neurologic examination, and if the muscles tested for the ergogram were representative, the myasthenia was still mild.

The findings on the lumbar puncture were normal; therefore, neurosyphilis is excluded as a cause for the cranial-nerve paralysis in view of the fact that he had had no previous antisyphilitic treatment. The x-ray films of the mediastinum were normal. Presumably, this examination included fluoroscopy, which is the most reliable means of detecting enlargement of the thymus gland. The gastrointestinal series was primarily concerned with the diagnosis of cancer. No mention was made of a barium-swallow examination, which I suspect would have been negative. Perhaps this would be a good time to see the x-ray films.

DR. C. C. WANG: We do not have the fluoroscopic report about the swallowing mechanism of this patient, but one can see the pyriform sinuses and the hypopharynx markedly distended with air; the esophagus is also filled with air to an unusual extent. These findings are consistent with myasthenia gravis. The lung fields are generally large and bright. There is marked increase of pulmonary markings; overlying these markings in the lower lobes are ill defined, nodular shadows of varying sizes with multiple radiolucencies suggesting bronchiectasis. The heart is not enlarged; the mediastinum is of normal width. The upper gastrointestinal series is not remarkable except for an abnormal amount of air in the esophagus.

DR. TIMBERLAKE: Apparently, there was doubt about the adequacy of the dosage of neostigmine on admission. When that is so it is better to underdose, avoid solanaceous drugs and, if respiration becomes difficult, use a respirator. Tracheotomy should be done early as an elective procedure. Respiration and swallowing are the only vital functions affected by myasthenia. It does not affect the heart or smooth muscles. If the patient cannot swallow, he can be tube fed. A myasthenic patient can, if necessary, be carried for months in a respirator until a remission or cautious gradual adjustment of medication has given him good strength.

This patient's neostigmine was increased fivefold on the first hospital day. Side effects are not mentioned, but he was given 6 tablets of ephedrine — a large dose, particularly for an elderly man with evidence of arteriosclerosis. On the next day the dose of neostigmine was considerably reduced for reasons not given, but apparently he still needed all but 1 of the ephedrine tablets. On the fourth day neostigmine was cut to 4 tablets, but again only a slight reduction was made in the ephedrine.

Time does not permit a discussion of the possible relation of the unknown amount of thyroid that was given to stimulate the appetite. I doubt if it played a significant part in the final episode.

On the fifth day he was given an enema. When a myasthenic patient is poorly controlled an enema is a hazardous procedure. When absolutely necessary an enema should be small in amount and gently administered, and timed so that its effect coincides with the time of optimum effect of the neostigmine. We do not know just how an enema upsets a precariously balanced myasthenic patient. Perhaps the enervating effect of the purgation is responsible. Perhaps it is the release of an excess of acetylcholine by concomitant parasympathetic reaction. Perhaps less direct endocrine reactions are important.

The patient became cold and sweaty, with nasal secretions and drooling from the mouth. No doubt, tracheal and bronchial secretions were also increased in this man, whose lungs were compromised by disease. Apparently, the drooling was the result of parasympathetic stimulation, not pharyngeal weakness, for he swallowed a whole glass of water. He was given neostigmine. This would have constricted bronchioles and increased bronchial secretions, aggravating the vicious circle of anoxemia and pulmonary edema. Cyanosis increased. Cerebral anoxemia was manifested by the obtundation of the patient, and cerebral edema probably developed. I should not be surprised if there was a cerebellar pressure cone. Shock increased. The atrial activity was not described, and so I can say nothing more on that point.

In summary, this patient with mild myasthenia gravis had pulmonary fibrosis, bronchiectasis and probably arteriosclerotic heart disease. Pneumonia may have increased the myasthenia slightly, but its major effect was interference with respiration. I think he was overdosed with neostigmine and ephedrine. An enema precipitated an irreversible reaction, with increased bronchial secretions, anoxemia, pulmonary edema and very probably cerebral edema. The toxic effect of the ephedrine on the heart was the final blow.

DR. BENJAMIN CASTLEMAN: I gather that Dr. Timberlake's statements will require a word from Dr. Schwab.

DR. ROBERT S. SCHWAB: This man was one of the early patients in our myasthenia-gravis clinic. When he was first seen he was severely myasthenic, being unable to work and unable to swallow, and having ptosis. He was given neostigmine, and within fifteen minutes he was jumping around effortlessly and picking up tables. His response was one of the most dramatic that we have ever seen. He was given 10 or 12 tablets a day. He returned to work as a baker, and carried around sacks of flour weighing 80 to 90 pounds. Four or five years later he had a remission and was taking only 3 or 4 tablets a day. I saw him again eight or nine years later; then I doubted if he had any myasthenia, for he did not respond to neostigmine. I believe the weakness was from other medical causes. When I saw him while he was in the hospital for the last time, I was skeptical that he had myasthenia because the difference between the performances with and without medication was insignificant.

DR. ALFRED KRANES: Would you amplify Dr. Timberlake's comment on the toxicity of neostigmine?

DR. SCHWAB: As Dr. Timberlake pointed out, this is an anticholinesterase drug, which effectively neutralizes about 90 per cent of the symptoms of myasthenia gravis. If it is given in excess to myasthenic patients, however, it produces another type of end-plate block, a depolarizing block in which the impulse cannot get through, and paralysis and weakness occur rapidly. Death from overdosage of neostigmine has been reported a number of times by several clinics. The drug produces this block in normal patients at a much lower level. This drug, given above its effective curative level, becomes a dangerous poison. As Dr. Timberlake pointed out, if the warning gastrointestinal toxic effects are masked with an atropine drug, dangerous poisoning may result. The early signs of overdosage are usually cold sweating, miotic pupils, hyperperistalsis, diarrhea, cramps and excessive pulmonary and tracheal secretions. Then come weakness and fasciculations of the muscles, and finally paralysis and death. Those signs are typical of a cholinergic crisis. It is interesting that the patient was able to tolerate 30 tablets of neostigmine a day for long periods during the early admission without severe side effects. He had a fairly high level of tolerance to the drug even in the terminal illness.

DR. CASTLEMAN: Do you think that he did not die in a myasthenic crisis?

DR. SCHWAB: I am certain that he did not die in a myasthenic crisis. It was not clear in the mimeographed sheet whether the 15 mg. of neostigmine administered on the fifth day after the episode of diarrhea, and so on, was injected or given by mouth. There is about a 12:1 effective difference between intramuscular and oral administration. That is a tremendous dose. I do not believe that I have ever given that much.

DR. RALPH WILLIAMS: That was given by mouth about two hours before death. I should like to add that on the first day of admission he received 75 mg. of ephedrine and only 90 mg. of neostigmine, not 450 mg. as stated in the protocol.

DR. SCHWAB: Fifteen mg. given orally is perfectly safe for a normal person; this patient may have had cramps. He weighed only about 90 pounds on admission. (He was a huge 180 pounder when we first saw him.) The drug effect is more critical with severe underweight and malnutrition.

DR. CASTLEMAN: Dr. Schwab, do you, like Dr. Timberlake, believe that the cause of the patient's death was an overdose of neostigmine?

DR. SCHWAB: Not if the 15 mg. was given by mouth. I do not think the injection immediately before death had any effect. I do not think he died from either cholinergic or myasthenic crisis.

DR. CASTLEMAN: What do you think caused death?

DR. SCHWAB: I think that he had a cardiac lesion, not on a pharmacologic basis — possibly thrombosis.

DR. JACOB LERMAN: It is difficult to explain the heart block on the basis of ephedrine.

DR. RICHARD B. COHEN: A condition that should be considered in patients who die suddenly with myasthenia gravis is the severe myocarditis that is present in some of these cases. We have found this lesion in about 20 per cent of cases autopsied in the past twenty years, and a number of them showed severe

myocardial damage. Several reports of this entity have appeared in the literature.[1] It is possible that myocarditis is responsible for some of the sudden deaths that have been attributed to myasthenic crisis and overdosages of drugs, and its possible presence should be considered in the clinical handling of the severely ill myasthenic patient.

DR. SCHWAB: In 1939 we[2] studied 12 myasthenic patients with electrocardiograms before and after neostigmine; I do not think that we had any post-mortem material. We had the opposite impression — that is, at the stage of the disease when the patients were ambulatory, there was no evidence of myocardial abnormality in the electrocardiogram. Whether the patients who die while the disease is acute have myocardial changes as a result of the myasthenia is still a question.

DR. COHEN: The myocarditis is often severe but tends to occur in a patchy, disseminated pattern. I think it might be missed on electrocardiograms.

DR. LAWRENCE H. WARBASSE, JR.: This patient's final collapse followed the administration of an enema. I do not know whether these events were causally related. However, there are two forms of collapse that may occur in such patients: vasovagal syncope and a shocklike state resembling water intoxication. The latter has been described by Hiatt[3] in patients with congenital megacolons, most of whom were receiving neostigmine medication and tap-water enemas. His studies clearly show that the sudden weakness, pallor, excessive sweating and occasional vomiting are related to precipitous falls in plasma sodium, chloride and protein concentration. Although I do not know whether such a sequence of events occurs in a patient with a normal colon, it seems reasonable to assume that it may. Dr. Hiatt believes that such catastrophes may be avoided by the use of isotonic solutions in enemas.

DR. CASTLEMAN: This patient had had severe chronic constipation for years; terminally, the large bowel was distended with feces, but we certainly would not call it Hirschsprung's disease.

DR. FRANK K. AUSTEN: We hear a great deal about focal myocarditis in patients dying with myasthenia gravis, infectious polyneuritis, poliomyelitis and other conditions of known or unknown etiology in which the patient may well be dying in a state of anoxia. I wonder if focal mononuclear-cell infiltrations, the most common pathological finding, actually represent a myocarditis or are merely concomitant to an anoxic death.

DR. COHEN: I think that an important point is that a severe myocarditis may occur, no matter what its etiology. From its appearance on histologic examination — the severe focal muscle damage, the peculiar histiocytic infiltration and in some cases fibrosis — I would say that anoxia as a cause was unlikely, but, of course, I cannot completely exclude it.

CLINICAL DIAGNOSES

Pulmonary embolus or myasthenic (gravis) crisis.
Chronic pulmonary fibrosis and emphysema with chronic bronchitis and bronchiectasis.
Pernicious anemia, treated.
Late, latent syphilis.

DR. WILLIAM H. TIMBERLAKE'S DIAGNOSES

Myasthenia gravis, mild.
Pulmonary fibrosis.
Bronchiectasis.
? Arteriosclerotic heart disease.
Pneumonia.
Neostigmine and ephedrine intoxication.

ANATOMICAL DIAGNOSES

Myasthenia gravis, sixteen years.
Thymoma.
Bronchopneumonia.
Bronchiectasis, moderate.
Pulmonary emphysema and fibrosis, severe, chronic.
Annular calcification of mitral valve.
Fecal impaction of rectum and descending colon.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: I am afraid that I am not going to be able to answer the questions about the cause of the patient's death. We were under the impression that he had died of a myasthenic crisis. We found a great deal of bronchiectasis and a fair amount of bronchopneumonia. I believed that the infection precipitated a more severe myasthenia than he had had in the past and that that had caused death.

DR. SCHWAB: The patient swallowed, talked and had no ocular signs during the final episode. If those critical muscles are not involved, the patient does not die with myasthenia.

DR. CASTLEMAN: The heart was not enlarged; it showed mild to moderate coronary-artery disease; there were no occlusions of the coronary vessels. He did have a thymoma. The tumor was 3.5 to 4 cm. in diameter and showed microscopically the characteristic changes of a thymoma — lymphocytes and epithelial cells. I am still disturbed because before this conference I assumed that the patient had died in myasthenic crisis precipitated by infection in the lungs, and now I think that perhaps he did not. I do not know what caused the death.

DR. KRANES: There is no way of deciding that anatomically.

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MASSACHUSETTS MEDICAL SOCIETY
1781 - 1956

EIGHT score and fifteen years ago, health being considered as "essentially necessary to the happiness of society," a bill to incorporate certain gentlemen as the Massachusetts Medical Society was introduced in the Massachusetts House of Representatives. The bill had its first reading on May 11, 1781, its second on June 6 and its third on June 7, when it was ordered to lie until September 15, on which date it had its final reading and its passage. Two days later it was amended and approved by the Senate; the amendment was accepted by the House, which in turn amended it on October 30. As it accumulated speed the bill was accepted by the Senate on November 1 and on the same day received the signature of Governor John Hancock. By such processes the Society came into being; less than a year later a faculty of medicine was established by Harvard College.

The detailed story of the country's early medical societies is told in Burrage's *History of the Massachusetts Medical Society.** Boston may apparently claim the honor, if such it is to be considered, of having been the birthplace of the first of these associations, in 1735-1736. This attempt having died in its infancy the next appears to have been "A Society of Gentlemen in New York, founded about 1749, for the weekly discussion of Medical Subjects." No further mention is made of this cultural organization.

In 1765 Cotton Tufts, of Weymouth, made the first effort at organizing a state society in Massachusetts; the plan was abortive, but in the following year one was successfully established in New Jersey. Since the New Jersey Society suspended operations from 1795 to 1807, however, the Massachusetts Medical Society takes precedence as the oldest in continuous existence. In 1765, the same year that Cotton Tufts made his unsuccessful attempt at organization, Dr. John Morgan, returning from Europe, founded the Philadelphia Medical Society, which in 1768 merged with the American Society for the Promotion of Useful Knowledge. This group, initiated by Benjamin Franklin, later became the American Philosophical Society, the oldest learned society in the country in continuous existence.

Two organizations established in Boston in 1780 were more or less closely related to the Massachusetts Medical Society. These were the Boston Medical Society, which seems to have been its direct progenitor, and the American Academy of Arts and Sciences, whose original membership overlapped that of the Society and whose charter is similar enough to have been drafted by the same hand.

Scarcely more than a week after the incorporation of the Society, a call for a first meeting was sent out by Dr. E. A. Holyoke, of Salem, on November 9.

*Burrage, W. L. *A History of the Massachusetts Medical Society, 1781-1922*. 505 pp. Privately printed, 1923.

The meeting was held on November 28 at the County Court House in Boston, and Holyoke, whose black silhouette is so familiar to those who are interested in such objects of art, was elected president. The first of the long succession of annual meetings was held on June 5, 1782.

The only serious threat to the Society's function of officially representing the medical profession of Massachusetts was made in 1811. In that year 12 malcontents, styling themselves the Massachusetts College of Physicians, petitioned the legislature for a charter as a competitive organization. They were later joined by Benjamin Waterhouse, "always happiest when in the opposition," but despite this reinforcement the petition was denied.

A hundred and seventy-fifth anniversary is not reckoned in figures sufficiently round to make it either here or there in a program of temporal events. For those who were too young to participate in the Society's sesquicentennial celebration, however, and those who for one reason or another expect to miss the bicentenary observance it may serve as a satisfactory stopgap.

TREATMENT OF VENTRICULAR FIBRILLATION

ACUTE cardiac arrest constitutes one of the most difficult and challenging emergencies. It may be due to ventricular standstill or ventricular fibrillation. Although frequent in acute myocardial infarction, in advanced coronary atherosclerosis and in many toxic states, it also occurs occasionally in patients during operations when the heart has been considered to be normal.

The emergency is so urgent that treatment must be instituted within three minutes if it is to be successful. When the emergency situation arises during a thoracic or abdominal operation, manual massage of the heart may be effective for either standstill or ventricular fibrillation. Under other circumstances, however, open thoracotomy must be resorted to without delay.

In the laboratory animal, ventricular fibrillation may be stopped, or atrial or ventricular contractions may be stimulated, by direct application to the heart of electric impulses of the proper type.

In 1952 Zoll* first reported successful stimulation of the heart in 2 patients with complete heart block and cardiac standstill by means of electric impulses applied externally to the chest wall. Subsequent experience has verified the usefulness of this procedure in ventricular standstill of any cause.

Elsewhere in this issue of the *Journal* the successful termination of ventricular fibrillation is reported by external chest application of high-voltage alternating current for fifteen hundredths of a second. The use of these high, potentially dangerous countershock voltages must be surrounded by adequate precaution by the medical personnel. Although such externally applied countershock has been previously successful in terminating ventricular fibrillation in the laboratory animal, this has not heretofore been shown to be feasible in man. External countershock can be applied easily and quickly, but delay in its application constitutes a major limitation. In the 3 patients who died, circulation had been ineffective for seven minutes or more before defibrillation. It is to be anticipated, moreover, that since ventricular fibrillation tends to occur in hearts severely affected by coronary-artery disease and acute myocardial infarction and as a terminal event in toxic states, ultimate survival of the patient will inevitably be infrequent even though the arrhythmia is abolished. The patient who survived three distinct episodes was alive and well some months later. This procedure may well prove to be of value in relation to surgery in poor-risk patients with continuous electrocardiographic monitoring.

Of considerable interest is the possible wider application of this therapeutic technic. Thus, ventricular tachycardia was stopped on one occasion in Case 4, and atrial fibrillation, atrioventricular nodal tachycardia and ventricular tachycardia have been terminated in the laboratory animal by this means.

External electric stimulation and defibrillation comprise a combined technic for resuscitation of patients from cardiac arrest in the operating room, in seriously ill patients or in other circumstances when emergency thoracotomy is inadvisable.

*Zoll, P. M. Resuscitation of heart in ventricular standstill by external electric stimulation. *New Eng. J. Med.* **247**:768-771, 1952.

CATASTROPHES OF 1955

A CATASTROPHE, according to the statisticians of the Metropolitan Life Insurance Company, is an accident in which 5 or more lives are lost; a major catastrophe entails a mortality of 25 or over. Catastrophes caused about 1500 deaths in the United States during 1955, or approximately 300 more than in 1954. The increased toll is a result of the increase from 4 major catastrophes in 1954 to 9 in 1955.

Five of 1955's major catastrophes were classed as natural disasters — meteorologic disturbances in which man and his works happened to be in the way of aberrant forces as yet uncontrolled. The most violent of these phenomena was the hurricane Diane and its accompanying floods, with a toll of 180 lives. Other major disasters caused by nature in excitation were the Midwestern tornadoes of May 25 with 115 deaths; the Christmas floods in California and Oregon, with an estimated toll of 84; the October floods in the Northeast with a mortality of 48; and the hurricane Connie, in which 25 lives were lost. The disasters for which man and his works were accountable included a hotel fire in Chicago in which

29 persons perished, and three plane crashes in which 124 were killed.

On the world stage 1956 is off to a bad start with the unprecedentedly catastrophic winter in Europe and an early list of plane and train disasters that speak ill for man's manipulation of the products of his own eccentric genius.

WOCHENSCHRIFT AUF ENGLISCH

THE little group of venerable but sprightly weekly medical journals of the English-speaking world have considered as a near cousin, even if discoursing in a different language, the *Deutsche Medizinische Wochenschrift,* now in its eighty-first year. It is not difficult, therefore, for them to be in sympathy with the suggestions that have been made for an English translation of the *Wochenschrift* and to applaud the decision of the editors and publishers to perform this service for their interested English-reading colleagues wherever they may be.

Under the title *German Medical Journal* the new publication, the first issue of which has already made its appearance, will consist rather of a monthly English-language edition of the *Wochenschrift* than a complete translation. It will contain not only the most important articles from the *Wochenschrift* but in addition will attempt to provide a general picture of German medical science and practice. Much of this material will have been prepared especially for the *German Medical Journal.*

The editor of the new edition is G. R. Graham, of London, the publisher Georg Thieme Verlag, Herdweg 63, Stuttgart.

The editor of the Buffalo Medical Journal calls attention to the change which has of late taken place in the treatment of phthisis, and bears testimony to the beneficial effects of alcoholic liquors in moderate doses, combined with a nourishing diet, and active, and even violent exercise in the open air.

Boston M. & S. J., *April 24, 1856*

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room, Hotel Statler, Boston, on Monday, May 21, at 5 p.m.

Business:

1. Call to order at 5:00 p.m.
2. Presentation of record of meeting held February 1, 1956, as published in Vol. 254, Supplement No. 1, March 15, 1956, of the *New England Journal of Medicine.*
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary

COMMITTEE ON MATERNAL WELFARE

POST-PARTUM HEMORRHAGE FROM ATONY OF THE UTERUS

A thirty-nine-year-old gravida X, para IX, had had an uneventful prenatal course. All previous deliveries had been at home, several of them being breech presentations.

The patient entered the hospital at term in labor with the breech presenting. After eight hours, a double-footling breech was seen at the vulva, with the umbilical cord protruding. Under light ether anesthesia, a living infant weighing 3.8 kg. (8 pounds, 8 ounces) was easily delivered. An apparently intact placenta was delivered about ten or fifteen minutes later. There were no lacerations, and the patient did not bleed excessively immediately after the third stage was completed.

About an hour post partum, she was in shock, with a weak pulse, no obtainable blood pressure and poor color. Her physician, still in the hospital, was called and expressed a large amount of clots from the uterus and vagina. Ergot was given intravenously, and a saline infusion started. The pulse was recorded as 100, and the blood pressure as 40 systolic, ?diastolic. Intermittent bleeding associated with an enlarged, soft fundus occurred during the next hour. The fundus responded temporarily to repeated oxytocics, but bleeding recurred shortly after their administration.

Two hours post partum, a transfusion was started, and the vagina packed, because bleeding continued. Half an hour later, a consultant was called. He arrived in about another half-hour, to find the vagina being repacked, since the original packing had become saturated. A second 500 ml. of blood was now started. The patient was in extremis, without regular respirations, pulse or blood pressure. The fundus was just below the umbilicus and fairly firm. She was pronounced dead three hours and forty-five minutes after delivery.

This was classified as a preventable death due to post-partum hemorrhage from atony of the uterus. The primary avoidable factors were delay in treatment and inadequate transfusion.

It is notorious that grand multiparas, particularly those who have had large infants, are especially prone to post-partum atony and hemorrhage. The obstetrician should therefore take unusual precautions after

expulsion of the placenta to prevent exactly the accident that occurred in this case. Prudent practice demands that the fundus be held for no less than forty-five minutes post partum in *all* deliveries. This not only guards the fundus against filling up but also makes the onset of shock immediately apparent. Additional minimal measures include ample intravenous administration of ergot after delivery of the placenta, supplemented by intramuscular doses and, failing the efficacy of these, intravenous administration of diluted posterior pituitary extract given through a slow drip. The omission of these precautions in the case under discussion was unfortunate.

One cannot help wondering how closely the patient had been observed during the first hour and how much visible blood there was, as well as how long she had been in shock before it was noted. Hospital personnel may have been negligent or incompetent; even so, at this juncture the patient's life might have been saved by prompt and copious use of whole blood. Hospitals where deliveries are carried out should have emergency blood immediately available, but in the case under consideration, instead of blood, saline solution was given. Although the record indicates continued bleeding, blood was not given for fully an hour. Furthermore, it is stated that a *vaginal* pack was inserted — also two hours post partum. This procedure is open to two criticisms: a pack in the vagina hides but does not stop further bleeding; and the treatment was begun too late. The record states that half an hour after this, a consultant was called, arriving three hours post partum. Obviously, the patient's doom had been sealed before he arrived, and it is not remarkable that his efforts were in vain. The fact that the vagina was being repacked when he arrived illustrates the futility of vaginal packing. If any pack was indicated in this patient, it should have been intra-uterine and should have been inserted immediately at the first evidence of hemorrhage — that is, an hour post partum when she was found in shock.

In summary, then, post-partum hemorrhage from atony should have been anticipated, and appropriate measures taken. Failing that, immediate, copious transfusion and intra-uterine packing should have been started at the first sign of persistent hemorrhage. Further blood for transfusions and a competent consultant should have been called at that time rather than several hours later.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATHS

BINNEY — Horace Binney, M.D., of Milton, died on March 19. He was in his eighty-second year.

Dr. Binney received his degree from Harvard Medical School in 1901. He was professor of surgery, emeritus, at Tufts University School of Medicine, a trustee of the Boston Medical Library, a fellow of the American Medical Association and the American College of Surgeons and a member of the American Surgical Association and the New England Surgical Society.

He is survived by his widow, two daughters and a sister.

STIFFLE — Abraham M. Stiffle, M.D., died on March 17. He was in his fifty-fourth year.

Dr. Stiffle received his degree from Tufts College Medical School in 1928. He was head of the St. Luke's Hospital clinic for alcoholism, special examiner for the Massachusetts Department of Mental Health, Division of Defective Delinquents, clinical director at Taunton State Hospital in charge of all psychiatric care and treatment and a member of the Massachusetts Society for Research in Psychiatry, American Psychiatric Association and the New England Society of Psychiatry.

He is survived by his widow, his mother, a brother and a sister.

NOTICES

HARVARD MEDICAL SOCIETY

A program presented by the Undergraduate Assembly of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, May 8, at 8 p.m. Spencer Gordon will act as presiding officer. The program is as follows:

Effect of Cardiac Glycosides on Potassium Transport in Human Red Cells. Thomas J. Gill. Harvard Medical School. Class III.

Effect of Hypothermia on the Electrical and Mechanical Activity of the Dog Ventricle, Studied in Situ. Leon I. Goldberg. Harvard Medical School. Class IV.

Studies on Atrioventricular Conduction in Man. Hershel Jick. Harvard Medical School. Class IV.

Glycerol Dissimulation in *Acetobacter suboxydans*. David Korn. Harvard Medical School. Class II.

Detection and Inactivation of the Virus of Homologous Serum Hepatitis. Joseph P. O'Malley. Harvard Medical School. Class IV.

Fine Structure of the Neurosecretory System of the Blue Crab. Elenore R. Sade. Harvard School of Dental Medicine. Class IV.

The Effect of Tranquilizing Agents on the ACTH Response to Stress. Herbert Wells. Harvard School of Dental Medicine. Class IV.

The Soma Weiss Award will be presented by the Faculty Committee.

BOSTON BRANCH, AMERICAN MEDICAL WOMEN'S ASSOCIATION

A luncheon and meeting of the Boston Branch of the American Medical Women's Association will be held at the Hotel Statler, Boston, on Wednesday, May 23, at 12 noon.

Dr. Esther Marting will talk on the subject "The Aims and Purpose of the Association."

AMERICAN COLLEGE OF CARDIOLOGY

The fifth annual convention of the American College of Cardiology will be held at the Hotel Drake, Chicago, Illinois, May 16-18. Topics of the meeting will be in the form of three symposiums on congestive heart failure, cor pulmonale and cardiac catheterization and angiocardiography. In addition there will be scientific sessions on all aspects of research, diagnosis and therapy, scientific exhibits on cardiovascular research and commercial exhibits outlining the latest advances in cardiology. Further information may be obtained from Dr. Philip Reichert, Secretary, American College of Cardiology, Empire State Building, New York City, New York.

MASSACHUSETTS HEART ASSOCIATION

The sixth in the series of "Stump the Cardiologist" meetings, sponsored by the Massachusetts Heart Association, will

be held in the Jimmy Fund Auditorium, Binney Street, Boston, on Wednesday, April 25, at 8 p.m.

Dr. Herrman L. Blumgart will discuss and answer questions on "Cardiac Pain."

AMERICAN ASSOCIATION FOR CLEFT PALATE REHABILITATION

The fourteenth annual meeting of the American Association for Cleft Palate Rehabilitation will be held at the Muehlebach Hotel, Kansas City, Missouri, May 3-5.

AMERICAN ASSOCIATION OF ORTHODONTICS

The annual meeting of the American Association of Orthodontics will be held at the Hotel Statler, Boston, April 29 through May 3. The program will include papers and clinics on the management of cleft palate, child growth and development, anthropometrics and orthodontic diagnosis and treatment.

Members of the medical, dental and allied professions who are interested in attending the meeting may obtain further information from Dr. A. D. Pierce, Chairman, 59 Federal Street, Greenfield, Massachusetts.

ARMED FORCES INSTITUTE OF PATHOLOGY

A postgraduate course on diseases of the heart, sponsored by the Armed Forces Institute of Pathology, will be held at the Institute, Washington, D.C., May 14-17. The four-day course will deal with heart disease from various clinical aspects as well as from the pathological point of view. The course will be open to a total of 425 civilian physicians and physicians in the armed forces. Civilian physicians desiring to attend may apply to the Director, Armed Forces Institute of Pathology, Washington 25, D.C.

SOCIETY MEETINGS AND CONFERENCES

April 19 and 20. American College of Allergists. Page 399, issue of February 23.

April 19-21. American Academy of Pediatrics. Page 399, issue of February 23.

April 22. Massachusetts Chapter, American Academy of General Practice. Page 676, issue of April 5.

April 23-26. International Academy of Proctology. Page 399, issue of February 23.

April 24 and May 3. Boston City Hospital House Officers' Association. Page 725, issue of April 12.

April 25. Soldiers Home, Chelsea. Page 676, issue of April 5.

April 25. Massachusetts Heart Association. Page 773.

April 25-27. Lectures on Radiobiology. Page 726, issue of April 12.

April 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

April 29-May 3. American Association of Orthodontics. Notice above.

May 1-5. Sixth National Congress on Pediatrics. Page 491, issue of March 8.

May 2. Postgraduate Medical Institute. Page 487, issue of September 15.

May 3-5. American Goiter Association. Page 348, issue of August 25.

May 3-5. American Association for Cleft Palate Rehabilitation. Notice above.

May 8. Harvard Medical Society. Page 773.

May 14-17. Armed Forces Institute of Pathology. Notice above.

May 14-18. American Nurses' Association. Page 491, issue of March 8.

May 16-18. American College of Cardiology. Page 773.

May 22-24. Massachusetts Medical Society Annual Meeting.

May 23. Boston Branch, American Medical Women's Association. Page 773.

May 28-June 1. European Symposium on Vitamin B. Page 578, issue of September 29.

June 1-9. International Medical-Surgical Meetings. Page 540, issue of March 15.

June 4-13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

June 21-23. Society of Nuclear Medicine. Page 1092, issue of December 15.

June 21-24. American Academy of Dental Medicine. Page 944, issue of December 1.

August 19-23. American College of Chest Physicians. Page 840, issue of November 10.

September 3-5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.

September 10-14. American Dietetic Association. Page 1180, issue of December 29.

Calendar for the Week Beginning Thursday, April 26

Thursday, April 26

Phi Delta Epsilon Fraternity Graduate Club Program. Dance.

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.

*8:45-9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00-10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00-10:00 a.m. Grand Rounds, Russell Room, House of Good Samaritan.

*10:00-11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Guest Speaker of the Bingham Associates. Genitourinary Problems in Children. Dr. Orvar Swenson. Cape Cod Hospital, Hyannis.

*11:00 a.m.-12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.

*11:00 a.m.-12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.-12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.

*12:00 m.-1:00 p.m. Staff Conference. Hypothermia. Dr. A. F. Heganauer. Stearns Auditorium, New England Center Hospital.

*12:15-1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

*3:00 p.m. Thoracic Conference. Surgical Metabolism As It Relates to the Care of the Cardiac Patient. Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*4:30 p.m. Lecture on Radiobiology. Radiation Hazards. Outpatient Lower Amphitheater, Massachusetts General Hospital.

Friday, April 27

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30-11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.

*12:00 m. Urological Conference. Dr. C. J. E. Kickham. Auditorium, Carney Hospital, Dorchester.

*1:00-3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*2:00-3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.

*4:00-6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Lecture Hall, Pratt Diagnostic Hospital.

*4:00-10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

*4:30 p.m. Lecture on Radiobiology. Newer Concepts of Radiation Illness and Its Treatment. Outpatient Lower Amphitheater, Massachusetts General Hospital.

Saturday, April 28

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30-10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:30-11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.

10:00 a.m.-1:15 p.m. Boston City Hospital Alumni Association Clinical Meeting. Boston City Hospital.

*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, April 30

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30-9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.

*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*2:00-3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.

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